DEC 20 1919

VOLUME 24 NUMBER 6

ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston
LOUIS V. HAMMAN, Baltimore
GEORGE DOCK, St. Louis
WARFIELD T. LONGCOPE, New York
W. S. THAYER, Baltimore

DECEMBER 15, 1919

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

AUGUST, 1919. NUMBER 2

Immunity of City-Bred Recruits. A. G. Love, M.D., and Charles B. Davenport, M.D., Washington, D. C.

Pathologic Anatomy and Bacteriology of Influenza. Epidemic of Autumn, 1918. Baldwin Lucke, M.D. (Philadelphia); Toynbee Wight, M.D. (Santa Monica, Calif.), and Edwin Kime, M.D. (Indianapolis), Camp Zachary Taylor, Ky.

A Study of the Incidence of Pulmonary Tuberculosis in Soldiers with Irritable Hearts. John T. King, Jr., M.D. (Baltimore), Lakewood, N. J.

The Increase of Extract Nitrogen in the Tissues, with Chronic Nephritis. Nellis B. Foster, M.D., New York.

SEPTEMBER, 1919. NUMBER 3

Studies on Epinephrin. I. Effects of the Injection of Epinephrin in Soldiers with "Irritable Heart." Joseph T. Wearn, M.D. (Charlotte, N. C.) and Cyrus C. Sturgis, M.D., (Pendleton, Ore.), Lakewood, N. J.

Studies on Epinephrin. II. The Effects of Epinephrin on the Basal Metabolism in Soldiers with "Irritable Heart," in Hyperthyroidism and in Normal Men. Edna H. Tompkins (Cambridge, Mass.), Cyrus C. Sturgis, M.D. (Pendleton, Ore.) and Joseph T. Wearn, M.D. (Charlotte, N. C.), Lakewood, N. J.

Studies on Epinephrin. III. Effect of Epinephrin on the Electrocardiograms of Patients with "Irritable Heart." Harry D. Clough, M.D. (Providence, R. I.), Lakewood, N. J.

An Experimental Endothelial Leukocytosis in Guinea-Pigs. Fifth Report of Studies on the Mononuclear Leukocytes of the Blood. Frank A. McJunkin, M.D., and Alice G. Charlton, M.A., Milwaukee.

Necropsy Studies at a Hospital Center. Moses Barron, M.D., St. Paul.

The Possibilities of Physical Development in Cases of Effort Syndrome by Means of Graded Exercises. Bertnard Smith, M.D., Los Angeles.

Experimental Emphysema. Sarah R. Kelman, M.D., Iowa City.

A Preliminary Survey of the Thyroid Gland Among Twenty-One Thousand One Hundred and Eighty-Two Recruits at Camp Lewis, Washington. William J. Kerr, M.D., San Francisco.

OCTOBER, 1919. NUMBER 4

The Production of Bright's Disease by Feeding High Protein Diets. L. H. Newburgh, M.D., Ann Arbor, Mich.

Cutaneous Reaction and Desensitization in Quinin Idiosyncrasy. John J. O'Malley, M.D., and DeWayne G. Richey, M.D., Washington, D. C.

Protozoologic and Clinical Studies on the Treatment of Protozoal Dysentery with Benzyl Benzoate. I. A Preliminary Report on Eight Cases of Endamebic Dysentery Treated at the Philippine General Hospital. Frank G. Haughwout, M.D., and Pedro T. Lantin, M.D., Manila, P. I., with an Addendum by M. A. Asuzano, M.D., Baguio, P. I.

A Statistical Discussion of the Relative Efficiency of Different Methods of Treating Pneumonia. Raymond Pearl, Baltimore.

The Basal Metabolism in Hypothyroidism. J. H. Means, M.D., and J. C. Aub, M.D., Boston.

The Relation of Neurocirculatory Asthenia to Hyperthyroidism as Determined by the Effects of the Injection of Epinephrin. Ernest P. Boas, M.D., New York.

The Significance of Abnormalities in the Form of the Electrocardiogram. G. Canby Robinson, M.D., St. Louis.

The Use of Laboratory Methods in the Diagnosis of Early Hyperthyroidism. Charles W. Lueders, M.D., Philadelphia.

The Control of Acidosis in the Treatment of Diabetes. Edgar Stillman, M.D., New York.

Sino-Atrial Heart Block in a Child. With Observations on the Effects of Atropin and Vagus Stimulation. N. Worth Brown, M.D., Baltimore.

NOVEMBER, 1919. NUMBER 5

Factors Determining the Relative Intensity of the Heart Sounds in Different Areas. An Experimental Study. Carl J. Wiggers, M.D., Cleveland.

Prolongation of the "S-T" Interval of the Ventricular Complex as Shown by the Electrocardiograph. Jonathan Meakins, M.D., Montreal, Can.

Progressive Lenticular Degeneration Associated with Cirrhosis of the Liver (Wilson's Disease). C. P. Howard, M.D., and C. E. Royce, M.D., Iowa City, Iowa.

The Energy Index (S.D.R. Index) of the Circulatory System. Joseph H. Barach, M.D., Pittsburgh.

Meningococcus Meningitis at Camp Lee. Russell L. Haden, M.D. (Detroit), Camp Lee, Va.

The Cholesterol Content of the Blood in Various Hepatic Conditions. M. A. Rothschild, M.D., and J. Felsen, M.D., New York.

Three Cases of "Renal Glycosuria." Frederick M. Allen, M.D., Mary B. Wishart and L. Millard Smith, Lakewood, N. J.

A Group of Sixty-Eight Cases of Type I Pneumonia Occurring in Thirty Days at Camp Upton. With Special Reference to Serum Treatment. Charles F. Tenney, M.D. (Toledo), and William T. Rivenburgh, M.D. (Highland, N. Y.), Camp Upton, N. Y.

The Determination of Hemoglobin by the Acid Hematin Method. Louis Berman, New York.

A Study of the Renal Concentration Power for the Uric Acid in Early Chronic Interstitial Nephritis. Preliminary Paper. Roy Upham, M.D., and Henry Allen Higley, M.D., Brooklyn.

Roentgenographic Studies in Gout. C. W. McClure, M.D., and E. D. McCarty, M.D., Boston.

COPYRIGHT, 1919, BY THE AMERICAN MEDICAL ASSOCIATION

Archives of Internal Medicine

Vol. 24 DECEMBER, 1919 No. 6

BOTULISM

A STUDY OF THE RESISTANCE OF THE SPORES OF BACILLUS BOTULINUS TO VARIOUS STERILIZING AGENCIES WHICH ARE COMMONLY EMPLOYED IN THE CANNING OF FRUITS AND VEGETABLES *

ERNEST C. DICKSON, M.D., GEORGINA S. BURKE, A.M.
AND
ENGELENA S. WARD, A.M.
SAN FRANCISCO

In view of the increasing frequency with which, during recent years, it has been shown that outbreaks of food poisoning affecting human beings and domestic animals or fowl have been caused by the ingestion of *B. botulinus* toxin in canned foods, it was considered advisable to make an investigation of the resistance of the spores of *B. botulinus* to various sterilizing agencies which are commonly employed in canning foods. Our interest in the problem was stimulated by the fact that in our investigations of a number of outbreaks of fatal poisoning which had occurred on the Pacific Coast,[1, 2] it was found that practically all had been caused by the ingestion of home canned vegetables and fruits; and in investigating the methods of canning which had been employed in preserving the food it was found that no one method was at fault. Our investigations showed that foods which had been canned by the one period sterilization process, with or without the addition of lemon juice, by the fractional method of sterilization or by a combination of the hot pack and cold pack processes had all, in certain instances, contained a potent toxin of *B. botulinus*. It is unfortunate that in many instances the persons who canned the food

* From the Laboratory of Experimental Medicine, Leland Stanford Junior University School of Medicine.

* Aided by a grant from the California State Council of Defense.

* The experiments described in this paper were performed during the year 1917-1918, but on account of war conditions it was not possible to publish the results at that time.

1. Dickson, E. C.: Botulism. A Clinical and Experimental Study, Morographs of the Rockefeller Institute for Medical Research, No. 8.

2. Dickson, E. C.: Botulism. A Further Report of Cases Occurring in the Pacific Coast States, Arch. Int. Med. **22**:483 (Oct.) 1918.

were victims who succumbed to the poisoning, and it was impossible to obtain exact data as to the canning methods employed, but in other instances we were able to learn the exact procedure in all its detail and to verify by laboratory tests that if the spores of *B. botulinus* were added to the raw material the methods were not efficient to the extent that they destroyed the spores.

Our experiments were performed with the hope that we might learn something of the reason why these various methods of canning may be inefficient, and thereby be able to devise some alterations which might render them efficient under all conditions. It must be admitted that up to the present time our results have not led to the evolution of safer methods, but it must be emphasized that it has not been our purpose merely to accumulate data which may be used for destructive propaganda, but that we have attempted to ascertain the facts which it is essential to recognize if we are to hope to be able to control food poisoning of this type.

The experiments may be divided roughly into two groups: (*a*) experiments to test the degree of resistance of the spores of *B. botulinus* to various sterilizing agencies, such as exposure to heat or to the action of dilute acid (lemon juice) or sugar at varying temperatures or in varying concentrations; and (*b*) tests of various methods of canning vegetables or fruits which we had contaminated with the spores of *B. botulinus;* but in several instances we have described experiments of each group under a single subheading for greater convenience in description. In all our experiments we made careful controls and deduced our conclusions only after repeated observations had been made.[3]

A. *Experiments to determine the thermal death point of spores of B. botulinus under conditions analogous to those which obtain when they are mixed with food material.*

The spores of eight strains of *B. botulinus* were used in these experiments, Strains I and II, which are old laboratory stock cultures, III, V and VIII, which we isolated from spoiled home canned string beans, VI (the Niven strain), which was recovered from cheese, VII, which we obtained from spoiled home canned asparagus, and IV, which we recovered from home canned corn. Strains III, IV, V, VI and VII were recovered from food which had produced fatal poisoning of human beings, and strain VIII from material which had poisoned a number of chickens. With the exception of strains I, II and V, all produce a highly potent toxin when grown on suitable

3. These investigations have been carried further by one of us and some of the later observations have already been published. Burke, G. S.: The Effect of Heat on the Spores of Bacillus botulinus, J. A. M. A. **72**:88 (Jan. 11) 1919.

culture mediums. The spores were obtained in strains I to VII, inclusive, by incubating the respective strains in brain medium at 26 C. for at least six weeks, and in strain VIII from a jar of string beans which had been canned by Mrs. M. at Berkeley, Calif. (2. Sect. B. Outbreak 1). The brain mediums and the beans were thoroughly mashed and diluted with normal salt solution to a fluid consistency. By this procedure we obtained an admixture of spores and animal or vegetable protein, an intimate association simulating that which exists when food material is contaminated with spores.

TECHNIC

Ten c.c. of each spore bearing mixture was placed in thin glass test tubes which were immersed into water in a water bath in such a manner that the surface of the fluid in the tubes was at least two inches below the surface of the water. A constant temperature was maintained at the degree required in each experiment, and test inoculations were made from each tube every fifteen minutes, the portion for inoculation being removed by a glass pipet which had been heated to the temperature of the contents of the tube, and transferred to freshly boiled deep glucose agar tubes. The culture tubes were sealed with wax to prevent drying, and were incubated at 26 C. They were examined daily for two weeks, after which, if there was no visible growth, they were discarded. The results of the experiments[4] are shown in Tables 1, 2 and 3.

The results obtained in these experiments are of considerable interest because of the demonstration that, when mixed with an animal or a vegetable protein, the spores of *B. botulinus* are extremely resistant to heat. This observation is entirely at variance with the statement which is found in all the textbooks, where the thermal death point of the spores of this bacillus is given at exposure to 80 C. for one hour. The fact that all the strains survived after being heated at 90 C. for three hours, that seven survived after being heated at 95 C. for three hours, and that six survived immersion in boiling water for two hours is ample proof that we are not dealing with a purely accidental observation. The significance of this high resistance, in so far as the canning of foods is concerned, will be considered under another section.

B. *Experiments to test the value of the addition of acid (lemon juice) to vegetables in so far as inhibiting the growth of B. botulinus is concerned.*

4. In the later experiments described by Mrs. Burke it was found that after being heated the spores sometimes remain quiescent for considerably longer than two weeks, hence in the present experiments it is possible that a larger percentage of positive subcultures would have been obtained had we not discarded our tubes in two weeks.

TABLE 1.—Showing the Effect when Spores of B. Botulinus Mixed with Animal or Vegetable Protein Are Immersed in Water at 90 C. for Three Hours

Inoculation Time	Strain							
	I	II	III	IV	V	VI	VII	VIII
Control*	1 day	1 day	3 days	3 days	1 day	4 days	1 day	3 days
15 minutes	1 day	1 day	4 days	3 days	1 day	3 days	—	5 days
30 minutes	1 day	1 day	3 days	3 days	1 day	4 days	7 days	4 days
45 minutes	2 days	1 day	3 days	3 days	2 days	4 days	7 days	8 days
60 minutes	1 day	1 day	3 days	4 days	1 day	3 days	—	9 days
75 minutes	2 days	1 day	4 days	4 days	2 days	3 days	—	8 days
90 minutes	1 day	1 day	4 days	5 days	1 day	3 days	—	8 days
105 minutes	2 days	1 day	4 days	5 days	2 days	3 days	—	10 days
120 minutes	1 day	1 day	3 days	5 days	1 day	3 days	6 days	8 days
135 minutes	2 days	1 day	4 days	8 days	1 day	3 days	—	—
150 minutes	2 days	2 days	5 days	5 days	2 days	4 days	10 days	—
165 minutes	2 days	2 days	5 days	5 days	2 days	4 days	10 days	—
180 minutes	2 days	2 days	5 days	5 days	2 days	3 days	3 days	11 days

* The control inoculations were made as soon as the contents of the tubes had risen to that of the surrounding water. The spores of Strains I to VII inclusive were mixed with brain medium, those of Strain VIII with crushed canned string beans.

The number of the days recorded is that on which the characteristic growth with fragmentation of the medium by gas was first observed.

TABLE 2.—Showing the Effect when Spores of B. Botulinus Mixed with Animal or Vegetable Protein Are Immersed in Water at 95 C. for Three Hours

Inoculation Time	Strain							
	I	II	III	IV	V	VI	VII	VIII
Control	1 day	1 day	1 day	2 days	1 day	1 day	2 days	2 days
15 minutes	1 day	1 day	3 days	2 days	1 day	1 day	2 days	2 days
30 minutes	1 day	2 days	3 days	3 days	2 days	2 days	3 days	4 days
45 minutes	2 days	2 days	5 days	3 days	2 days	2 days	5 days	4 days
60 minutes	2 days	2 days	6 days	4 days	2 days	2 days	5 days	5 days
75 minutes	2 days	2 days	10 days	4 days	2 days	2 days	6 days	3 days
90 minutes	2 days	2 days	11 days	4 days	2 days	2 days	6 days	4 days
105 minutes	3 days	2 days	11 days	5 days	2 days	2 days	6 days	5 days
120 minutes	3 days	2 days	—	6 days	2 days	2 days	6 days	4 days
135 minutes	4 days	3 days	—	—	3 days	3 days	7 days	8 days
150 minutes	5 days	2 days	—	—	3 days	3 days	7 days	4 days
165 minutes	3 days	3 days	—	8 days	3 days	3 days	8 days	6 days
180 minutes	2 days	2 days	—	—	4 days	3 days	7 days	12 days

TABLE 3.—Showing the Effect when Spores of B. Botulinus Mixed with Animal or Vegetable Protein Are Immersed in Boiling Water for Two Hours

Inoculation Time	Strain							
	I	II	III	IV	V	VI	VII	VIII
Control	1 day	1 day	3 days	1 day	1 day	1 day	2 days	3 days
15 minutes	2 days	2 days	5 days	3 days	2 days	2 days	4 days	5 days
30 minutes	2 days	3 days	6 days	5 days	2 days	2 days	4 days	9 days
45 minutes	2 days	3 days	8 days	4 days	2 days	3 days	—	5 days
60 minutes	3 days	7 days	10 days	6 days	7 days	4 days	5 days	5 days
75 minutes	2 days	—	10 days	—	2 days	2 days	6 days	5 days
90 minutes	3 days	—	—	—	2 days	2 days	7 days	5 days
105 minutes	4 days	—	—	4 days	6 days	2 days	8 days	5 days
120 minutes	13 days	—	—	4 days	2 days	2 days	13 days	11 days

In Circular No. 158 of the University of California Agricultural Experimental Station, W. V. Cruess describes a modification of the one period method of sterilization which "consists essentially of making the vegetables slightly acid, thus rendering them as easy to sterilize as fruits." In discussing his method on page 4 of the circular, Cruess writes: "It was found that peas heated to 212 F. in a brine acidified by the addition of five ounces of lemon juice to every gallon kept perfectly, while peas heated in the same brine, without the lemon juice, spoiled. The same results were obtained with beans, pumpkins, beets, turnips, artichokes and asparagus."

Three sets of experiments were undertaken:

1. To test whether lemon juice in the concentration recommended by Cruess will of itself inhibit the growth and toxin formation of *B. botulinus;*

2. To test whether varying concentrations of lemon juice will lower the thermal death point of spores of *B. botulinus;* and

3. To test whether the actual method of canning which Cruess recommends is efficient if the raw material is contaminated with spores of *B. botulinus.*

1. EXPERIMENTS TO TEST WHETHER LEMON JUICE BRINE IN THE CONCENTRATION RECOMMENDED BY CRUESS WILL INHIBIT THE GROWTH AND TOXIN FORMATION OF B. BOTULINUS.

Technic. — Beef infusion broth was prepared according to the formula recommended by van Ermengem,[5] and sufficient quantities of salt, sugar and lemon juice were added to make up acid broth brines of the same concentration as Cruess recommends for green peas and string beans respectively. (Peas: 2⅓ ounces salt, 3½ ounces sugar and 7 ounces lemon juice per gallon; Beans: 2½ ounces salt, 5 ounces sugar and 5 ounces lemon juice per gallon). The medium was thoroughly boiled and cooled, inoculated with washed bacilli (*B. botulinus,* strain III) and covered with liquid petrolatum. Control tubes of plain van Ermengem broth were prepared and inoculated, and all the tubes were incubated at 26 C. for about six weeks. Subcultures were then made to demonstrate the presence of living bacteria, and after filtration through diatomaceous filters, the lemon juice-brine broth was tested for the presence of toxin. Guinea-pigs weighing from 200 to 275 gm. were used for the inoculations. The results of the experiment are tabulated in Table 4.

The experiment shows that lemon juice brine, in the concentration recommended by Cruess for peas and beans, does not prevent the

5. Van Ermengem, E.: Der Bacillus botulinus und der Botulismus: in Kolle, W., and von Wassermann, A., Handbuch der pathogenen Mikroorganismen, Jena, Ed. 2, **4**:909, 1912.

growth of *B. botulinus* nor the development of the toxin, notwithstanding the fact that the optimum reaction for the development of botulinus toxin is neutral or slightly alkaline. However, the amount of toxin developed in both brines was considerably less than occurred in the control van Ermengem broth.

TABLE 4.—SHOWING THE EFFECT ON THE GROWTH AND TOXIN FORMATION WHEN B. BOTULINUS IS INCUBATED IN LEMON JUICE BRINE-BROTH

Mediums*	Bacteria Recovered	Toxin Tests				
		Animals Died in				
		1 C.c.	0.5 C.c.	0.002 C.c.	0.001 C.c.	0.0005 C.c.
Control broth	Yes	—	—	—	—	48 hours
Peas brine	Yes	16 hours	16 hours	21 hours	Survived	Survived
Beans brine	Yes	16 hours	16 hours	21 hours	Survived	Survived

* The brine-broths contain the concentrations of lemon juice and salt which Cruess recommends for canning peas and beans respectively.

2. EXPERIMENTS TO TEST THE EFFECT OF VARIOUS CONCENTRATIONS OF LEMON JUICE ON THE THERMAL DEATH POINT OF SPORES OF B. BOTULINUS.

Technic.—To a series of test tubes containing each 10 c.c. of a diluted brain medium culture of *B. botulinus* (strain III) in which were numerous spores, sufficient lemon juice was added to make a concentration of 25, 12.5, 6.25, 3.12 and 1.56 per cent. lemon juice respectively. These tubes, together with a control tube to which no lemon juice had been added, were immersed in a water bath (as in experiments described in A) which was kept at a constant temperature of 80, 90, 95 and 100 C., respectively, during the various investigations. Beginning with the time at which the mixture in the tubes had reached the temperature of the surrounding water, and at fifteen minute intervals thereafter throughout the experiments, test inoculations were made into deep glucose agar, as in section A. The subcultures were examined daily for the appearance of visible growth and fragmentation of the medium, but when still negative on the sixteenth day they were discarded. The results of the experiments are tabulated in Tables 5, 6, 7 and 8.

The experiments show that the addition of lemon juice to a mixture of spores of *B. botulinus* in brain medium, i. e., animal protein, has a very definite effect in lowering the thermal death point of the spores. In Table 5, where the mixtures were submitted to a temperature of 80 C., although the spores survived for three hours in all concentrations of lemon juice, there was a definite and progressive delay in growth after heating in the higher concentrations of lemon juice, probably indicating that the spores were damaged although not killed. In Tables 6, 7 and 8, where the mixtures were submitted to temperatures of 90, 95 and 100 C., respectively, there was indication that the

TABLE 5.—SHOWING THE EFFECT OF SUBMITTING SPORES OF B. BOTULINUS WHICH ARE MIXED WITH ANIMAL PROTEIN, AND IN THE PRESENCE OF VARYING CONCENTRATIONS OF LEMON JUICE, TO A TEMPERATURE OF 80 C.

Time of Inoculation	Percentage Lemon Juice					
	25 per Cent.	12.5 per Cent.	6.25 per Cent.	3.12 per Cent.	1.56 per Cent.	n/salt
Control	3 days*	3 days	3 days	3 days	3 days	3 days
Heated						
15 minutes	6 days	3 days	3 days	3 days	3 days	3 days
30 minutes	6 days	4 days	3 days	3 days	3 days	3 days
45 minutes	6 days	4 days	3 days	3 days	3 days	3 days
60 minutes	8 days	4 days	3 days	3 days	3 days	3 days
75 minutes	9 days	4 days	3 days	3 days	3 days	3 days
90 minutes	10 days	6 days	3 days	3 days	3 days	3 days
105 minutes	10 days	6 days	3 days	3 days	3 days	3 days
120 minutes	6 days	6 days	3 days	3 days	3 days	3 days
135 minutes	16 days	8 days	3 days	3 days	3 days	3 days
150 minutes	9 days	8 days	3 days	3 days	3 days	3 days
165 minutes	—	8 adys	3 days	3 days	3 days	3 days
180 minutes	10 days	10 days	3 days	3 days	3 days	3 days

* The number of days indicates, in each case, the time at which visible growth with fragmentation of mediums was first observed.

TABLE 6.—SHOWING THE EFFECT OF SUBMITTING A MIXTURE OF SPORES OF B. BOTULINUS IN ANIMAL PROTEIN AND LEMON JUICE TO A TEMPERATURE OF 90 C.

Time of Inoculation	Amount Lemon Juice					
	25 per Cent.	12.5 per Cent.	6.25 per Cent.	3.12 per Cent.	1.56 per Cent.	n/salt
Control	5 days	4 days	4 days	Contaminated	4 days	4 days
Heated						
15 minutes	N. G.*	N. G.	8 days	4 days	4 days	4 days
30 minutes	N. G.	N. G.	11 days	5 days	4 days	4 days
45 minutes	N. G.	N. G.	N. G.	8 days	4 days	4 days
60 minutes	N. G.	N. G.	N. G.	N. G.	6 days	4 days
75 minutes	N. G.	N. G.	N. G.	N. G.	—	4 days
90 minutes	N. G.	N. G.	N. G.	N. G.	8 days	4 days
105 minutes	N. G.	N. G.	N. G.	N. G.	8 days	4 days
120 minutes	N. G.	N. G.	N. G.	N. G.	10 days	4 days
135 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	4 days
150 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	4 days
165 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	4 days
180 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	4 days

* N. G. indicates that there was no growth or fragmentation visible in 16 days.

TABLE 7.—SHOWING THE EFFECT OF SUBMITTING A MIXTURE OF B. BOTULINUS IN ANIMAL PROTEIN AND LEMON JUICE TO A TEMPERATUURE OF 95 C.

Time of Inoculation	Amount Lemon Juice					
	25 per Cent.	12.5 per Cent.	6.25 per Cent.	3.12 per Cent.	1.56 per Cent.	n/salt
Control	6 days	5 days	4 days	3 days	3 days	3 days
15 minutes	N. G.	N. G.	N. G.	9 days	5 days	3 days
30 minutes	N. G.	N. G.	N. G.	9 days	6 days	5 days
45 minutes	N. G.	N. G.	N. G.	N. G.	8 days	5 days
60 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	6 days
75 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	10 days
90 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	10 days
105 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	11 days
120 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	N. G.

higher the concentration of lemon juice the more readily were the spores destroyed, and in the instances where the spores survived, the length of time which elapsed before growth could be observed was roughly dependent on the concentration of the lemon juice, the length of the exposure to heat and the degree of heat.

3. EXPERIMENTS TO TEST THE EFFICIENCY OF THE PROCESS OF CANNING VEGETABLES BY THE ONE PERIOD METHOD OF STERILIZATION AFTER A GIVEN AMOUNT OF LEMON JUICE HAD BEEN ADDED TO THEM (CRUESS METHOD).

String beans and green peas were selected for the experiment and the directions given in the University of California Agricultural Experiment Station Bulletin No. 158, pages 28 and 29, were closely followed.

TABLE 8.—SHOWING THE EFFECT OF SUBMITTING SPORES OF B. BOTULINUS IN MIXTURE WITH ANIMAL PROTEIN AND LEMON JUICE TO THE TEMPERATURE OF BOILING WATER

Time of Inoculation	Amount Lemon Juice					
	25 per Cent.	12.5 per Cent.	6.25 per Cent.	3.12 per Cent.	1.56 per Cent.	n/salt
Control	5 days	5 days	3 days	3 days	3 days	3 days
15 minutes	N. G.	N. G.	7 days	6 days	5 days	5 days
30 minutes	N. G.	N. G.	N. G.	N. G.	7 days	6 days
45 minutes	N. G.	N. G.	N. G.	N. G.	12 days	8 days
60 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	10 days
75 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	10 days
90 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	N. G.

(a) *String Beans.*—The beans were washed, broken into pieces about 1½ inches long, blanched by dipping into boiling water for four minutes, chilled in cold water and packed into one quart Mason jars. During the process of filling the jars about 1 c.c. of a suspension of spores of *B. botulinus* (strain III) in salt solution was placed near the center of the jar. The beans were covered with boiling hot brine containing 2 per cent. salt and lemon juice in the proportion of 5 ounces per gallon, and sterilized covers were loosely applied. The jars were then immersed in boiling water in a wash boiler, and left for ninety minutes after the water recommenced to boil. At the end of the heating process the jars were removed, the covers tightened and the jars were placed in a dark closet.

(b) *Green Peas.*—The peas were shelled, blanched, packed and inoculated with a mixture of spores of *B. botulinus* (strain III) as were the beans, and were covered with a boiling hot brine containing 2⅓ ounces of salt, 3½ ounces of sugar and 7 ounces of lemon juice per gallon. The jars were left immersed in the boiling water in the wash boiler for one hour after the water recommenced to boil. They were then taken out, the covers were tightened and the jars were stored in a dark closet.

(c) *Controls.*—These were prepared by filling jars with blanched string beans in the same way as described in (a) with the exception that boiling water was substituted for the brine, and one teaspoonful of salt was added to each jar. In order that they might serve as a control for the one period cold pack process as well as for the method immediately under observation, the jars were left in the boiling water in the wash boiler for two hours, as recommended on page 17 of the U. S. Department of Agriculture, Farmer's Bulletin No. 839, instead of for ninety minutes as recommended by Cruess. The jars were then stored in a dark closet.

Results: After an interval of one month all the jars were opened. The peas and beans which had been canned by the Cruess method, with lemon juice, showed slight discoloration and one jar contained a mold, but cultures failed to show any growth of *B. botulinus*, and injection experiments failed to demonstrate the presence of toxin.

The contents of the control jars, on the other hand, contained very many spore bearing bacteria which were morphologically and culturally identical with the *B. botulinus* with which the beans had been inoculated, and injection of filtered juice into guinea-pigs demonstrated the presence of a highly virulent toxin.

The experiments indicate, therefore, that the Cruess method of canning vegetables with lemon juice is efficient even if the contents of the jars have been contaminated by spores of *B. botulinus* placed near the center of the jars. The control experiments provide further evidence that the wash boiler method of sterilization applied in the cold pack method of canning vegetables is inefficient under similar conditions.

It should be mentioned, however, that there is one recorded instance of fatal botulism intoxication from string beans which were canned "with some lemon juice," the amount of which could not be ascertained as the woman who canned the beans succumbed to the poisoning. (2. Sect. A, Outbreak 13).

C. *Experiments to test the efficiency of the fractional method of sterilizing vegetables which are contaminated with spores of B. botulinus.*

1. The method of fractional sterilization which was selected for investigation was that described by Breazeale in the U. S. Department of Agriculture Farmers' Bulletin No. 359. String beans were used for the experiment.

The beans were washed, broken into short pieces and packed into one quart jars, 1 c.c. of a mixture of spores of *B. botulinus* (strain III) being placed on the beans near the center of each jar. One level

teaspoonful of salt was added to each jar and cold water was added to fill the jars completely. The tops were applied loosely and the jars were placed in tepid water in a wash boiler which had a tightly fitting cover. The water in the boiler was gradually heated to boiling, and the jars were left in place for a full hour after the water had commenced to boil. The jars were then removed from the wash boiler and the tops were screwed tight. Half of the jars were allowed to remain at room temperature during the periods between sterilization, and the remainder were returned to the covered boiler where they cooled more gradually. On the second and third days the tops of the jars were loosened, and the process of heating was repeated. After the final sterilization, the tops were fastened tightly and the jars were placed in an incubator where they were left for one month in a temperature of 26 C.

When the jars were opened, the appearance of the contents was excellent, the odor was good, aerobic and anaerobic cultures showed no growth and injection of filtered juice with guinea-pigs failed to show the presence of toxin.

It would appear, therefore, that when followed carefully, the fractional method of sterilization in canning vegetables is efficient even though the raw material is contaminated with spores of *B. botulinus*. Attention should be drawn, however, to Case 3 in Section B. of a previous report[2] in which corn which was canned at home by this method contained a toxin which caused the death of a large number of chickens.

2. A second series of experiments was performed to test a method of fractional sterilization which is apparently in common use in certain sections of the country, and which we were requested to test. The method consisted of "blanching and packing vegetables into one quart jars and subjecting the sealed pack to a jumping boil for fifteen minutes on each of three successive days." As was to be expected, it was found that this method is totally inefficient if the raw material is contaminated with spores of *B. botulinus*.

D. *Experiments to test whether the presence of cane sugar in canned fruits will inhibit the growth of B. botulinus and the formation of its toxin.*

In a previous report[1] it was shown that infusions of apricots and peaches form a suitable medium for the growth of *B. botulinus* and for the formation of a virulent toxin, and subsequent experiments have shown that pears and prunes may also be employed in making suitable culture mediums. It became apparent, therefore, that the ordinary methods of canning should be investigated, especially since it is

believed that fruits require much less sterilization because of their acidity and because of the addition of sugar which is supposed to aid in preservation.

1. EXPERIMENTS TO TEST WHETHER CANE SUGAR IN DIFFERENT CONCENTRATIONS WILL PREVENT THE GROWTH AND TOXIN FORMATION OF B. BOTULINUS.

Beef broth was prepared according to the formula recommended by van Ermengem[5] with the exception that the 2 per cent. glucose was omitted, and sufficient quantities of cane sugar were substituted to form syrups of 12, 24, 35, 50 and 64 per cent., respectively, which are the concentrations of syrups recommended in the U. S. Department of Agriculture Farmers' Bulletin No. 839, page 14, for canning various fruits. The mediums were boiled and cooled, inoculated with a suspension of spores of *B. botulinus* (strains III and VI) which had been washed thoroughly in successive changes of physiologic solution of sodium chlorid to remove adherent toxin, covered with liquid petrolatum and incubated at 26 C. for one month. At the end of that time, subcultures were made, the syrups were passed through diatomaceous filters, and the filtrates were injected into guinea-pigs to test for the presence of virulent toxin. The results of these experiments are shown in Tables 9 and 10.

TABLE 9.—VALUE OF VARIOUS CONCENTRATIONS OF CANE SUGAR IN PREVENTING THE GROWTH AND FORMATION OF TOXIN OF B. BOTULINUS (STRAIN III)

Medium	Time of Growth	B. botulinus Recovered	Demonstration of Toxin	
			Guinea-pig Died in	
			0.5 C.c.	0.002 C.c.
2 per cent. glucose broth (control*)	1 month	Yes	16 hours	48 hours
12 per cent. cane sugar broth	1 month	Yes	16 hours	70 hours
25 per cent. cane sugar broth	1 month	Yes	18 hours	70 hours
35 per cent. cane sugar broth	1 month	Yes	18 hours	Survived
50 per cent. cane sugar broth	1 month	Yes	18 hours	Survived
64 per cent. cane sugar borth	1 month	Yes	18 hours	Survived

* The control glucose broth was of the same lot of broth as the cane sugar broth. Guinea-pigs weighing from 250 to 300 gm. were used in testing for toxin.

TABLE 10.—VALUE OF VARIOUS CONCENTRATIONS OF CANE SUGAR IN PREVENTING THE GROWTH AND FORMATION OF TOXIN OF B. BOTULINUS (STRAIN VI)

Medium	Time of Growth	B. botulinus Recovered	Demonstration of Toxin	
			Guinea-pig Died in	
			0.5 C.c.	0.002 C.c.
2 per cent. glucose broth (control)	1 month	Yes	16 hours	16 hours
12 per cent. cane sugar broth	1 month	Yes	16 hours	40 hours
24 per cent. cane sugar broth	1 month	Yes	16 hours	4 days
35 per cent. cane sugar broth	1 month	Yes	16 hours	40 hours
50 per cent. cane sugar broth	1 month	Yes	45 hours	Survived
64 per cent. cane sugar broth	1 month	Yes	42 hours	Survived

The experiments show conclusively that cane sugar in concentration up to 64 per cent. does not prevent the growth of *B. botulinus* or the formation of its toxin, although it does inhibit the toxin formation to a certain extent. In Table 9 it is shown that although 35, 50 and 64 per cent. cane sugar broths contain sufficient toxin to kill the guinea-pigs when 0.5 c.c. is injected, there is not sufficient toxin to kill when only 0.002 c.c. is injected; moreover, it is shown that although in 2 per cent. glucose broth culture grown for a similar length of time there is sufficient toxin in 0.002 c.c. to kill a guinea-pig in forty-eight hours in equal quantities of 12 and 24 per cent. cane sugar broths the amount of toxin present requires seventy hours to cause the death of the animal. Analogous results are shown in Table 10 when strain VI *B. botulinus* was used, although with this strain a more virulent toxin was obtained in 35 per cent. cane sugar broth than was the case with strain III.

2. Experiments to test whether fruits which had been canned in sugar form a suitable medium for the growth of B. botulinus and the development of its toxin.

In order that we might have as tests fruit in which there was presumably the optimum concentrations of syrup it was decided to use the highest grade of commercially canned goods which could be obtained in the market. Apricots, peaches and pears were selected, as in previous experiments we had found that infusions prepared from these respective fruits formed suitable mediums for toxin formation.

The tops of the cans were thoroughly washed, dried and burned over with alcohol to ensure sterilization of the surface. Small holes were punched with a sterilized file point, and through the punctures 1 c.c. of a suspension of thoroughly washed spores of *B. botulinus* (strain III) was introduced. The cans were resealed by soldering the punctures and were incubated at 26 C. for about three months. At the end of this time the cans were opened with sterile precautions, subcultures were made to test for the presence of living bacteria, and 1 c.c. of the syrup was injected into guinea-pigs to test for virulent toxin. The results of the experiments are shown in Table 11.

TABLE 11.—Fruits which Have Been Canned in Sugar Form a Suitable Medium for the Growth of B. Botulinus and the Formation of Its Toxin

Fruit	Time of Growth	Sub-cultures		Toxin in Syrup: Animals Died in
		Aerobic	Anaerobic	
Apricots I	3 months	No growth	B. botulinus	2 days
Apricots II	3 months	No growth	B. botulinus	2 days
Peaches I	3 months	No growth	B. botulinus	2 days
Peaches II	3 months	No growth	B. botulinus	1 day
Pears I	3 months	No growth	B. botulinus	2 days
Pears II	3 months	No growth	B. botulinus	2 days

The experiments show conclusively that apricots, peaches and pears which have been canned in sugar form suitable mediums for the growth of *B. botulinus* and the formation of its toxin, although the amount of toxin is very much less than is found when the organism is grown upon optimum medium.

E. Experiments to test the efficiency of the cold pack method of canning fruits, with or without the addition of sugar, when the raw material is contaminated with spores of B. botulinus. The wash boiler method of sterilization was used.

1. FRUITS CANNED WITHOUT SUGAR:

Peaches and prunes were selected for the experiment, and were as fresh as could be obtained in the open market. The fruit was canned according to the instructions given in the U. S. Department of Agriculture Farmers' Bulletin No. 839, page 15.

(a) *Peaches.*—The fruit was washed, pared and halved, the stones being discarded in half the jars and retained in the others, and after rinsing in cold water was packed into heated one quart Mason jars. About 1 c.c. of a suspension of spores of *B. botulinus* (strain III) was placed on the fruit near the center of each jar. The fruit was covered with boiling water, freshly boiled covers were applied and loosely fastened, and the jars were immersed in boiling water in a wash boiler where they were allowed to remain for thirty minutes after the water recommenced to boil. The jars were then removed from the wash boiler, the tops were tightened and the fruit was stored in a dark closet.

(b) *Prunes.*—The method of procedure was the same as that adopted with peaches, except that the fruit was not pared. The stones were removed in one half the jars and retained in the others. The duration of the sterilizing process was thirty minutes.

2. FRUITS CANNED WITH SUGAR:

Peaches and prunes were selected for these experiments also, which were run concurrently with those just described. The instructions given on pages 19 and 20 of Farmers' Bulletin No. 839 were closely followed.

(a) *Peaches.*—The method of preparing, packing and inoculating the fruit was identical with that described in the previous experiment, with the exception that boiling thin syrup, 16 per cent., was substituted for the boiling water. The jars were left immersed in boiling water for sixteen minutes, after which they were removed and stored in a dark closet.

(b) *Prunes.*—The method of procedure was the same as was adopted in the preceding experiment with prunes, except that the fruit

was covered with a medium thick syrup, 45 per cent., instead of with boiling water. The jars were left immersed in boiling water for sixteen minutes.

Results: After two months the jars were opened, aerobic and anaerobic cultures were made to demonstrate the presence of living bacteria, and guinea-pigs were injected to demonstrate the presence of toxin.

From all the jars we obtained pure cultures of *B. botulinus*, although in none of the jars was there toxin in the amount that 1 c.c. of the juice would cause any symptoms when injected into a guinea-pig. The fact that the bacteria had not lost the power of forming toxin was shown, however, by the fact that subcultures from the contents of the jars into glucose broth showed a vigorous growth and a highly potent toxic formation.

The experiments showed, therefore, that the period of sterilization was not sufficient to kill the spores of *B. botulinus*. The significance of the absence of toxin will be discussed later.

DISCUSSION

The observations recorded in the foregoing experiments assume considerable importance when we attempt to explain the causes of spoilage and the presence of botulinus toxin in canned vegetables and fruits. The recent noticeable increase in the number of outbreaks of botulinus intoxication[1, 2] in various portions of the United States[6] the great majority of which were caused by the ingestion of canned foods,[7] affords indisputable evidence that methods of canning which have hitherto been considered efficient are not efficient if the raw material happens to be contaminated with spores of *B. botulinus*.[8] It has become apparent from the distribution of outbreaks affecting human beings,[9] as well as from observations of Graham, Brueckner and Pontius[10] in outbreaks of forage poisoning in domestic animals, that the distribution of the *B. botulinus* is widespread throughout the

6. Curfman, G. H.: Botulism, Colorado Med. **15**:35 (Feb.) 1917.

7. McCaskey, G. W.: *Bacillus Botulinus* Poisoning, with a Report of Seven Cases, Four of which Proved Fatal, Am. J. M. Sc. **158**:57 (July) 1919.

8. Thom, C., Edmondson, Ruth B., and Giltner, L. C.: Botulism from Canned Asparagus, J. A. M. A. **73**:907 (Sept. 20) 1919.

9. In addition to the recorded cases we have record of seven more outbreaks occurring in the United States, and one in Yukon Territory in Canada in which human beings were poisoned.

10. Graham, L., Brueckner, A. L., and Pontius, R. L.: Studies in Forage Poisoning, VI, Bull. 208, Kentucky Agricultural Experiment Station. Graham, L., and Brueckner, A. L.: Studies in Forage Poisoning: The Relation of *B. Botulinus* to Forage Poisoning or Cerebrospinal Meningitis in Horses, J. Bacteriol. **4**:1 (Jan.) 1919.

country, and recent observations by one of us[11] give ample proof that the organism occurs in nature under conditions which are ideal for the contamination of foods such as are canned for human consumption.

The observations which were made concerning the thermal death point of spores of *B. botulinus* when mixed with animal or vegetable protein, a state of affairs which simulates that which exists when food materials are contaminated, are most striking. The description of *B. botulinus* which was elaborated by van Ermengem[5] and which has been universally accepted by all the authors of textbooks, states that heating to 80 C. for one hour will effectively destroy the spores, and, as a result, all methods of canning in which the sterilizing process has maintained a temperature which exceeded this have been considered safe in so far as *B. botulinus* is concerned. Our experiments show that the spores under conditions which simulate those which obtain when food material is contaminated will resist the temperature of boiling water for more than two hours, and of 95 C. for more than three hours, a fact that had not previously been suspected. Since it is impossible for the contents of a can or jar to assume a temperature higher than that of the surrounding medium, it is evident that any process of sterilization in which the temperature of boiling water is the highest temperature employed, the length of time necessary to sterilize the most accessible of the contents of the containers must exceed two hours, though how much more we have not yet determined. Moreover, it has been shown by various observers, that it requires an appreciable length of time for the contents at the center of the containers to reach the temperature of the surrounding medium. Bitting and Bitting[12] have studied this problem, and on page 32 of their report state: "The greatest factor affecting under-sterilization is the consistency of the material canned. . . . In experimental work it was found that the heat at the center of a No. 3 can containing water was raised from 85 to 210 F. in about four minutes after being dropped into the boiling water. The sweet potato (pie packed sweet potatoes) may require from three to four hours to reach a temperature above 200 F., and generally does not come within ten degrees of that of the bath during the whole process. In the former case, convection currents are established and the heat is conducted rapidly, in the latter no convection currents are present, and the broken, homogeneous mass acts almost as an insulating material for the central part."

11. Burke, Georgina S.: The Occurrence of *B. Botulinus* in Nature. In press (J. Bacteriol.).

12. Bitting, A. W., and Bitting, K. G.: Bacteriological Examination of Canned Foods. Research Laboratory National Canners' Association, Bull. No. 14, 1917.

It is evident, therefore, that when we depend upon the temperature of boiling water to effect complete sterilization of the contents of can or jar, we must make allowance for the fact that the contents at the center of the container are much more resistant to sterilization than those at the periphery. If we are to obtain complete sterilization at the center of the jar, it is necessary to leave the jar immersed in boiling water for a considerably longer time than that required to sterilize the contents at the periphery, the extent of the increase depending on the character of the food being canned.[13]

In our experiments with lemon juice the results were instructive in that they show conclusively that when exposed to certain degrees of acidity the spores of *B. botulinus* are readily destroyed by comparatively low temperatures. It has been emphasized by all previous workers that the toxin will not form in acid medium, but we have shown that this is not the case. Our first series of experiments show beyond all doubt that when exposed to brines containing salt in the amount of approximately 2 per cent. and lemon juice in the amount of approximately 5 per cent. a virulent toxin is developed under favorable conditions of temperature. But when the spores are exposed to the action of boiling water for one hour in acid brines of similar concentrations, as in the method of canning recommended by Cruess, or in a mixture of lemon juice of more than 2 per cent, as in our preliminary experiments, the spores are completely destroyed.

Another point of interest is that after prolonged heating, with or without the addition of lemon juice, the spores which survived were apparently damaged, since the length of time which elapsed before they germinated and grew was considerably prolonged. Whether this damage also affected the power of toxin formation has not been determined, although there is some evidence that this may be the case. In the experiments in which we tested out the cold pack method of canning fruit with or without sugar, it was found that living bacteria survived the process, although no toxin could be demonstrated in the syrup of the fruits. Subcultures of these bacteria in glucose broth produced a potent toxin, but it was not determined whether the toxin was present in as large amounts as ordinarily was formed in glucose broth. This point remained to be investigated.

The delayed germination of spores which had been exposed to prolonged heating may also be of importance in the efficiency of steriliza-

13. We have been severely criticized for invariably inoculating the contents of the jars near the center of the jars, but we believe that we were fully justified in doing so since it is at the center that there is the greatest danger that sterilization will be incomplete. If we are to accept any method of canning as entirely efficient we must assure ourselves that sterilization is complete in all parts of the container.

tion by the fractional method, since it is possible that their delayed germination may cause them to remain in a resistant stage when the subsequent exposures to heat are made. It is possible, however, that the damaged spore is more susceptible to heat than the normal spore, and our experiments with the fractional method of sterilization would seem to bear this out, since in all instances fractional sterilization by the standard method proved to be efficient. However, we believe that for successful sterilization by the fractional method, it is necessary that the jars be sealed tightly between the exposures to heat, as otherwise undamaged anaerobic spores would fail to germinate before the final sterilization.

The experiments concerning the effect of sugar in inhibiting the development of botulinus toxin are also of interest. The efficacy of the addition of sugar as in the old fashioned process of preserving fruit, where the sugar is added in large amounts, and the fruit is "boiled down" in the syrup is undoubted, as in such a process the temperature of the boiling material rises in proportion to the concentration of sugar attained by evaporation; but in the process of canning with sugar the temperature of the material in the containers cannot rise above that of the surrounding medium no matter what concentration of sugar is present. In canning fruits with sugar, therefore, the problem resolves itself into how much the addition of sugar in itself will aid in preventing the formation of toxin if the spore of *B. botulinus* happen to be present in the raw material and survive the processing. Our experiments showed that sugar in high concentration does not, of itself, prevent the growth of *B. botulinus* or the formation of its toxin, although it does inhibit the toxin formation to a certain extent. Moreover, they show that the finished product of certain fruits canned in syrup forms a suitable medium for growth and toxin formation. We did not have an opportunity of testing the effect of heating the spores in various concentrations of sugar as we tested the various concentrations of lemon juice.

As a result of our experiments we are forced to the conclusion that various factors which have been considered efficient in canning foods are inefficient if the raw material happens to be contaminated with spores of *B. botulinus;* and certain of our experiments have revealed facts which must affect the commercial canning processes as well as home canning methods. We have not had an opportunity of investigating the commercial canner's processes, but it is well known that they are not 100 per cent. efficient in preventing spoilage. The amount of spoilage varies considerably in different packs, according to Bitting,[14] that type of spoilage which he describes as "swells" being

14. Bitting, A. W.: The Canning of Foods, U. S. Dept. of Agriculture, Bureau of Chemistry, Bull. No. 151, 1912.

due to underprocessing and "more likely to be associated with rush operations."

Whether or not *B. botulinus* plays any important part in the causation of spoilage in commercially canned goods has not, in so far as we could learn, been determined. Weinzirl[15] in his report did not find *B. botulinus* in any of the cans which he examined, but since he discarded from his experiments all cans in which the contents were obviously unfit for food, his conclusions as to the complete absence of *B. botulinus* from commercial canned foods are scarcely justified. From his experiments he concludes that "commercial canned goods, as found in the markets, are not always sterile," and he assumes that "the living spores found in commercial canned foods are unable to grow in the food due to the absence of oxygen," but this can obviously only be interpreted to mean that in the cans which he examined he did not meet with any anaerobic spore bearing bacteria. There is nothing in his findings to indicate that had the raw material which was canned happened to be contaminated with spores of *B. botulinus*, the spores would not have survived and produced a virulent toxin.

In this respect the observations of Cheyney[16] are of even greater significance since his investigations were confined to commercially canned foods which were apparently fit for market. From his observation that an average of 8 per cent. of cans of food examined contained viable organisms (the percentage varied from 2 per cent. in apricots to 25 per cent. in crab), and that in a certain number of cans there was a pure culture of spore bearing bacteria, he concludes that the usual methods of processing are inefficient in that they do not result in complete sterilization. It is thus evident that in commercial canning processes as in home canning processes, the methods employed are not always efficient if the raw material happens to contain spores of *B. botulinus*.

Fortunately, the number of cases where canned foods have contained the botulinus toxin is comparatively very small; in fact, when we consider the tremendous amount of food material that is canned each year, the number of outbreaks of poisoning is exceedingly small. The greater number of outbreaks have been caused by the ingestion of home canned products, but the American medical literature contains at least two[6, 17] references, and we have record of a third case in which commercially canned goods are undoubtedly at fault. It is probable

15. Weinzirl, John: The Bacteriology of Canned Foods, J. M. Research **39**:349 (Jan.) 1919.

16. Cheyney, E. W.: A Study of the Micro-Organisms Found in Merchantable Canned Foods, J. M. Research **40**:177 (July) 1919.

17. Sheppard, C.: Report of Three Cases of Fatal Ptomain Poisoning, South. Calif. Pract. **22**:370, 1907.

that the repeated examinations of the commercial products for "swells" before they ultimately reach the consumer is a safe guard which is lacking in connection with the home canned product.

But even though the number of cases of poisoning caused by the ingestion of canned goods is small, they should not be disregarded. In view of the wide distribution of *B. botulinus* throughout the country it is important that the possibility of raw material being contaminated should always be borne in mind, and investigations should be undertaken to perfect methods of canning which will be efficient in destroying this resistant organism. Until this is done it will be necessary to instruct the public of the possible danger from existing methods of canning, and to urge that all canned food which shows the slightest sign of spoilage should be discarded. If all canned food is boiled before it is eaten, any possible danger of poisoning with botulinus toxin will be removed, as the toxin is destroyed by boiling.

CONCLUSIONS

1. The spores of *B. botulinus* when mixed with animal or vegetable protein are much more resistant to heat than has been believed.

2. The acidification of the culture medium by the addition of 5 per cent. lemon juice does not prevent the growth of *B. botulinus* or the formation of its toxin, but the thermal death point of spores of *B. botulinus* is markedly lowered when they are heated in an acid medium of similar concentration.

3. The addition of cane sugar to beef broth in concentration up to 64 per cent. does not prevent the growth of *B. botulinus* or the formation of its toxin, although it does inhibit both to a certain extent.

4. Certain fruits which have been canned in sugar form suitable mediums for the growth of *B. botulinus* and the development of its toxin. Peaches, apricots and pears were tested.

5. Certain of the methods of canning are inefficient if the raw material happens to be contaminated with spores of *B. botulinus*. This is true of commercial canners' processes as well as of the home canning processes.

A STUDY OF PNEUMOCOCCUS CARRIERS

JOSEPH SAILER, M.D.
Lieutenant-Colonel, M. C., U. S. Army
PHILADELPHIA

MILTON W. HALL, M.D.
Major, M. C., U. S. Army
CAMP JACKSON, S. C.

ROBERT L. WILSON, M.D.
Captain, M. C., U. S. Army
JEANNETTE, PA.

AND

CHARLES McCOY, M.D.
First Lieutenant, M. C., U. S. Army

During the winter of 1917-1918, 1,311 cases of pneumonia were treated at the Base Hospital, Camp Wheeler, Ga., with 275 deaths, constituting the largest mortality of any single disease in the camp, indeed, more than 80 per cent. of all the deaths that occurred. Control of the pneumococcus infections would obviously have saved many lives to the service and avoided as well the loss of a large number of men, who were later discharged on account of physical disability, the result of complications and sequels of pneumonia.

The unenviable eminence of this camp in the matter of pneumonia is undoubtedly due to a number of coinciding predisposing factors. Perhaps most important is the character of the men here in training during the winter under discussion. Vaughan and Palmer, in the course of their exhaustive investigation of the communicable diseases occurring in the army camps in this country, have shown that susceptibility to respiratory infections varies with the character of the environment from which the soldier comes, that men from rural homes are more susceptible than those from urban homes, and other things being equal, that the men of the South are more easily infected than those of the North. Camp Wheeler presented the unlucky condition of a command largely made up of rural Southerners. Conditions of clothing and shelter incidental to the early days of the mobilization undoubtedly played a part in determining the high incidence. Many cases followed measles, and the measles and pneumonia curves follow each other very closely. The short epidemic of influenza that visited the camp early in 1918 was followed by an increased number of cases of pneumonia.

Whatever combination of predisposing causes existed, it must in the end be evident that the cause of the disease in the individual man is infection by virulent micro-organisms, in this camp predominantly the pneumococcus in one or the other of its types. In each case so infected the main facts in the process have been two, the exposure of the man to the virulent organism, and his individual susceptibility to infection. In the protection of the individual, therefore, two distinctly differing methods present themselves. One concerns itself with the building up of individual resistance, and includes all the general hygienic methods at our disposal, and specifically in many diseases at least, the use of bacterial vaccines aiming to increase the antibody content of the blood. In pneumonia, the work of Lister in South Africa, of Cecil and Austin at Camp Upton, and the more extensive work done more recently under the army pneumonia commission promise results of value from this method. On the other hand, the workers at the Rockefeller Institute have shown, by means of specific type determinations on pneumococci, that contacts of pneumonia patients often become carriers of cocci of the same type as that infecting the patient, and clinical experience has long pointed to the conclusion that the disease exists at times as an epidemic, and that contact is an important factor in its dissemination.

In confirmation of this conclusion we present the following tabulation of cases occurring in one of the battalions of the 124th Infantry. This lists the cases of pneumonia in five companies by tents, giving in each case the date of onset and the type of pneumococcus discovered. Owing to press of work and scarcity of mice, type determinations were, at that time, done only in cases seriously ill.

Analysis of this table shows that of ninety cases reported from the battalion, fifty-four, or 60 per cent., occurred in tents reporting more than one case. The largest number from one tent was eight. Whether this suggests overcrowding or is due to the infection of successive inhabitants of the tent does not appear. The ninety cases occurred in fifty-three tents. The total number of inhabited tents in the battalion is not available at this time, but a minimum number possible can be obtained by adding the numbers of the highest numbered tents of each company reporting cases. This gives 119 tents. Therefore, we may say that of this number, sixty-six tents showed no cases; thirty-two tents, one case each; seven tents, two cases each; five tents, three cases each; one tent, four cases; one tent, five cases; one tent, six cases; one tent, eight cases. As to types of pneumococci, with but few exceptions the type is seen to be the same for any one tent. This result is the more interesting when the fact is noted that the typing was done in routine, without knowledge of the tent from which the man came,

and the data assembled some months later from the records. This should eliminate any chance of prejudice in interpreting results.

From this study it would appear that contact with infected individuals or carriers plays an important rôle in the spread of pneumonia, and if, therefore, the number of carriers of virulent pneumococci in a command could be reduced, there should follow a corresponding reduc-

TABLE 1.—PNEUMONIA CASES IN FIVE COMPANIES

Outfit	Tent No.	Date of Onset	Pneumococcus Type	Outfit	Tent No.	Date of Onset	Pneumococcus Type
Co. I	3	11/28/17	Undetermined	Co. L	3	11/24/17	Undetermined
	5	12/16/17	Undetermined		6	11/16/17	Undetermined
	7	10/28/17	Undetermined		9	11/21/17	Undetermined
	7	11/ 4/17	IV		10	11/ 5/17	IV
	8	10/22/17	IV		10	12/ 1/17	Undetermined
	8	11/15/17	Undetermined		14	11/13/17	Undetermined
	8	11/26/17	Undetermined		14	11/21/17	IV
	8	11/30/17	IV		14	12/13/17	Undetermined
	8	12/ 5/17	IV		16	11/29/17	Undetermined
	8	12/10/17	IV		20	12/31/17	Undetermined
	8	12/14/17	IV		21	11/ 9/17	Undetermined
	8	12/21/17	IV		21	1/27/18	IV
	10	11/26/17	IV		21	1/31/18	I
	10	1/14/18	Undetermined		24	11/23/17	Undetermined
	11	11/23/17	Undetermined		26	11/ 8/17	IV
	11	12/19/17	Undetermined		26	11/21/17	IV
	11	12/19/17	Undetermined				
	11	12/27/17	Undetermined				
	12	12/ 1/17	II	Co. M	1	4/14/18	Undetermined
	12	12/ 9/17	II		5	1/10/18	IV
	12	12/16/17	II		9	11/13/17	II
	12	12/21/17	II		11	11/17/17	IV
	12	12/30/17	II		11	1/10/18	IV
	12	2/ 1/18	II		13	11/10/17	Undetermined
	14	12/20/17	Undetermined		14	12/29/17	Undetermined
	14	3/ 3/18	Undetermined		16	11/23/17	IV
	18	10/28/17	IV		16	1/13/18	IV
	15	11/ 5/17	IV		18	11/15/17	Undetermined
	18	12/ 4/17	IV		20	11/23/17	Undetermined
					22	12/22/17	Undetermined
Co. K	3	11/ 7/17	Undetermined		22	11/26/17	Undetermined
	5	11/27/17	Undetermined		32	12/27/17	Undetermined
	9	10/29/17	Undetermined		33	12/26/17	Undetermined
	13	12/ 1/17	Undetermined		35	1/24/18	Undetermined
	16	11/16/17	III				
	17	12/ 5/17	II	Supply Co.			
	19	12/17/17	Undetermined		4	11/28/17	Undetermined
	20	12/ 1/17	Undetermined		6	12/ 1/17	Undetermined
	22	11/ 1/17	Undetermined		7	12/ 3/17	Undetermined
	28	11/23/17	II		7	1/13/18	IV
	28	11/25/17	I		7	1/22/18	IV
	28	12/ 4/17	I		8	11/23/17	Undetermined
	30	12/ 7/17	Undetermined		10	11/26/17	Undetermined
	31	11/13/17	I		11	11/26/17	IV
	31	11/26/17	I		12	12/21/17	IV
	31	1/18/18	I		13	1/23/17	IV
	31	1/18/18	I		19	3/18/18	I
	31	11/13/17	IV				

tion in the number of cases of pneumonia. Our problem, therefore, divided itself into two parts, the discovery of the carrier, and the devising of means of rendering him innocuous to others. The former fell naturally to the laboratory, the latter to the medical service.

The recognized method of detecting pneumococcus carriers by means of mouse inoculations, while undoubtedly the best from the standpoint of virulence determination, would not appear to be applic-

able to large numbers of men without the services of an impracticably large force of trained workers. We have therefore used a method, for which no claim of originality is made, which we believe fulfills the requirements of this work and is exceedingly simple in application and satisfactory in its results. It is based on the fact that the pneumococcus develops a green colony when grown on a blood agar plate, which enables us to select the colonies with ease, and to apply the technic of Avery for the determination of type. Briefly it is as follows. Swabs from the nasopharynx are spread on blood agar plates, and incubated for from sixteen to twenty hours. Characteristic colonies are picked and planted in the blood broth medium of Avery. Staining is unnecessary at this stage. After incubation the growth is examined by the Gram stain, tested for bile solubility, and the cultures that qualify are further tested for type by the precipitin method. Thus each organism recorded positive has shown characteristic morphology and staining reaction, given the green colony on blood agar, and proven soluble in bile.

We have used human blood for the plates and Avery tubes and found it equally as efficacious as that of the rabbit in promoting growth and developing the color. With that exception standard methods have been employed in the preparation of media.

It was early noted that a blood broth tube inoculated from a single colony was very much slower in developing sufficiently for use than one inoculated with emulsified sputum. To determine the optimum period of incubation under these circumstances, single colonies from seventeen different strains of pneumococcus were planted in Avery's broth, and from each tube smears were made and stained at intervals up to twenty-four hours. The results are shown in the following table.

TABLE 2.—GROWTH OF PNEUMOCOCCUS IN BLOOD BROTH

Incubation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1 hour	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2 hours	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3 hours	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0
4 hours	0	0	0	0	0	—	—	0	0	—	0	0	0	+	0	0	0
5 hours	0	+	0	+	0	+	+	+	+	—	—	0	+	+	+	+	—
6 hours	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+
8 hours	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+
9 hours	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+
11 hours	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+
21 hours	—	—	—	0	—	—	—	—	0	—	—	+	+	0	+	0	0
24 hours	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Under each number from one to seventeen is shown the result of the successive stains made from that tube. A zero indicates no visible growth on staining, a plus sign indicated the presence of gram-positive diplococci, while the minus sign indicates the presence of diplococci that decolorize by Gram's method. It is seen from the table that all

strains tested were autolyzed at the end of twenty-four hours, usually showing as gram-negative cocci at the examination preceding disappearance. Blood agar plates inoculated from the tubes at the end of the experiment remained sterile. Inasmuch as the bile solubility test is best applied to well preserved, actively growing cocci, the best length of incubation for this work would appear to be twelve hours.

After clearing with bile the growth is mixed with the standard dilutions of specific type sera and precipitin reactions noted. Results are uniformly clear cut and satisfactory.

In April, 1917, 700 men of the regiment mentioned above were examined by this method, one smear only being made from each man. The results are tabulated below.

TABLE 3.—Carriers Showing Type of Pneumococcus

	Number	Per Cent. of Total	Per Cent. of Carriers
Total Carriers	111	16.0	100.0
Carriers Type I	6	0.86	5.4
Carriers Type II	15	2.14	13.52
Carriers Type III	5	0.71	4.5
Carriers Type IV	85	12.1	76.58

This shows that 24 per cent. of the carriers and over 3 per cent. of the total number of men examined showed pneumococci of one or other of the so-called fixed types. These figures are higher than those generally accepted for the population as a whole, possibly because of the fact that the disease had been so prevalent in the organization examined in the preceding months, and many of the men were themselves recent convalescents.

The mere discovery of carriers does not promise any results of value. They must be isolated or the cocci removed from the air passages by some sort of antiseptic treatment. Isolation of 15 per cent. of a military command is obviously not a practical measure, and the problem presented to the medical service, therefore, was to find some means of sterilizing these men which should be practical, that is, easily applied by men of little training, effective and not particularly disagreeable to the subject. Further, it seemed desirable that, even if one successful method was discovered, other methods should also be tried, so that in the course of a campaign or on foreign service, if one method was not available another might be, and the work carried on in spite of limitations of material. Moreover, nothing should be done that was reasonably likely to impair the health or efficiency of the men.

By permission of the division surgeon, Lieut.-Col. Louis C. Duncan, the 111 men referred to above were admitted to the base hospital as pneumonia carriers, for the purpose of testing various methods of disinfection. To them were added several convalescent patients who still

harbored pneumococci. These men were placed in separate wards in groups of sixteen, and to each group was applied some method of treatment that seemed to promise results. This segregation was decided upon partly for the sake of control, partly for the purpose of preventing their conveying the infection to others. In order that the men might not become soft and acquire indolent habits, they were in the beginning given setting up exercises every day. Later a line officer was assigned to the convalescent wards and the men were kept fit by vigorous exercise and regular drill, so that on their return to their companies they were in better condition than when they were received.

No difficulty was experienced in persuading the men to undergo the treatment. They have all exhibited much cheerfulness. There have been no unpleasant results, except slight discomfort in one or two cases during chlorin gas treatment. These effects were of a temporary nature.

In detail the method adopted has been as follows: After a group of sixteen men had been assembled and the treatment decided on, the group was further divided into four squads of four men each. The same treatment was given to each squad, but the amount or frequency of the application varied. The treatments, as a rule, consisted of sprays or applications. The first squad was treated once daily, the second, twice, the third three times and the fourth four times, the purpose being to discover, if possible, the minimum treatment required. Cultures were made from these men at varying intervals, care being taken to obtain material in the early morning before any treatment had been received. When a man showed three negative cultures, he was regarded as clear and discharged. In some cases efforts have been made to have men report to the laboratory after some time had elapsed for the purpose of checking the ultimate result of treatment, but this has not been generally feasible. In one group no treatment was employed and cultures made to discover whether spontaneous clearing occurred.

The following is a list of measures employed:

1. Dichloramin-T dissolved in eucalyptol.
2. Dichloramin-T dissolved in chlorcosane.
3. Phenol in oil.
4. Phenol in glycerin.
5. Quinin sulphate.
6. Tincture of iodin in oil.
7. Chlorin gas.
8. Chloramin-T.
9. Eucalyptol.
10. Dobell's solution.
11. Chlorcosane.

RECORD OF EXPERIMENTS

EXPERIMENT 1.—Dichloramin-T in eucalyptol. Spraying with pressure tank at 20 pounds; 15 seconds in each nostril and 30 seconds in throat. Begun Feb. 3, 1918, ended Feb. 17, 1918. Ten men in three groups. Cultures taken February 7, 11 and 15.

First group, four men, sprayed once daily each. All cultures negative February 7 and 11. Treatment then suspended. February 15 two men failed to return, and two were negative.

Second group, four men, sprayed twice daily each. All cultures negative February 7 and 11. Treatment then suspended. All cultures negative February 11.

Third group, two men, sprayed four times daily. All cultures negative February 7 and 11. Treatment then suspended. Cultures negative February 15.

It was concluded that Dichloramin-T is an effective agent for destroying pneumococci in the nose and throat, and that two treatments per day gave the maximum efficiency. This experiment was repeated.

EXPERIMENT 2.—Exposure to chlorin gas in the gas chamber. The concentration was 1:45,000. The duration of exposure 30 seconds. Begun Feb. 20, 1918, ended March 3, 1918. Cultures were made on the second, fourth, sixth, eighth, ninth, eleventh, thirteenth and fifteenth days.

Squad 1, exposed on first day; Squad 2, exposed on first and third days; Squad 3, exposed on first, third and fifth days; Squad 4, exposed on first, third, fifth and seventh days. The results of the experiment are shown in Table 4.

TABLE 4.—RESULTS OF EXPERIMENT 2

	Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
No. 1	ex	0	..	0	..	0	..	+	0	..	0	..	0	..
No. 2	ex	0	..	0	..	0	..	+	0	..	0	..	+	..
No. 3	ex	0	..	0	..	0	..	0	0	..	+	..	+	..
No. 4	ex	0	..	0	..	0	..	0	0	..	+	..	+	..
No. 5	ex	0	ex	0	..	0	..	0	0	..	+	..	+	..
No. 6	ex	+	ex	0	..	0	..	0	0	..	+	..	+	..
No. 7	ex	+	ex	0	..	0	..	+	0	..	+	..	+	..
No. 8	ex	0	ex	0	..	0	..	0	0	..	+	..	0	..
No. 9	ex	0	ex	0	ex	0	..	+	0	..	+	..	0	..
No. 10	ex	+	ex	0	ex	+	..	+	0	..	+	..	0	..
No. 11	ex	+	ex	+	ex	0	..	0	0	..	+	..	0	..
No. 12	ex	0	ex	0	ex	0	..	0	0	..	+	..	0	..
No. 13	ex	0	ex	0	ex	0	ex	+	0	..	+	..	0	..
No. 14	ex	+	ex	0	ex	0	ex	0	0	..	+	..	0	..
No. 15	ex	0	ex	0	ex	0	ex	0	0	..	+	..	+	..
No. 16	ex	+	ex	0	ex	+	ex	+	0	..	+	..	+	..
No. 17	ex	0	ex	0	ex	0	ex	+	0	..	+	..	0	..

* "ex" indicates an exposure to chlorin gas; "0" a negative culture, and plus sign a positive culture.

This experiment is unsatisfactory. The series of negative results on the ninth day is doubtless due to technical error. Not all positive cultures were typed but in two instances types varied. Number 3 had a severe reaction from the gas and two others were made slightly uncomfortable so that we felt that the maximum dose had been employed.

On the whole, chlorin gas proved inefficient for the purpose and too dangerous for routine use.

EXPERIMENT 3.—Phenol (3 per cent.) in liquid petrolatum. Two drops were placed in each nostril and the throat swabbed at each treatment. Each man was treated twice daily. Begun March 11, 1918, ended March 27, 1918.

Squad 1, treated four days; Squad 2, treated eight days; Squad 3, treated twelve days; Squad 4, treated sixteen days. Cultures were made from all on the fifth, ninth, thirteenth and seventeenth days. All were negative with the exception of the second culture on Carrier No. 9, which yielded a pneumococcus Type I. Subsequent cultures in this case were negative.

It is therefore probable that this treatment is efficient for the purpose of destroying pneumococci in the nose and throat.

EXPERIMENT 4.—Five per cent. tincture of iodin in liquid petrolatum. Two drops in each nostril and the throat swabbed at each treatment. None of the men complained of discomfort at any time. Begun March 19, 1918, ended March 27, 1918.

Squad 1, one treatment daily for eight days; Squad 2, two treatments daily for eight days. Cultures on the fifth and ninth days. Numbers 1 and 4 were transferred to another camp at the end of eight days, and second cultures on them could not be obtained; otherwise all cultures were negative. This experiment was incomplete for reasons beyond our control, but suggests that 5 per cent. tincture of iodin in oil may be efficient.

EXPERIMENT 5.—Dichloramin-T, 2 per cent., dissolved in eucalyptol. After three days, the supply of the latter being exhausted, chlorcosane was substituted. The spray was used as in Experiment 1. Began April 3, 1918, ended April 14, 1918.

Squad 1, treatment once daily; Squad 2, treatment twice daily; Squad 3, treatment three times daily; Squad 4, treatment four times daily. Cultures were made on the fourth, seventh, tenth and twelfth days.

Squad 1, Nos. 1 and 2, were negative three times; not cultured on the twelfth day. No. 3 was negative on the first day; positive afterward, Type IV. No. 4 was positive in all cultures except the third.

Squad 2, Nos. 5 and 8, were negative three times, not cultured the fourth time. No. 6 was negative on the first and third culture, positive on the second; not cultured the fourth time. No. 7 was positive in all cultures except the second.

Squad 3, Nos. 9 and 11, were negative except in the third culture. No. 10 was negative in the first two cultures, positive in the last two. No. 12 was negative in three cultures; not cultured the fourth time.

Squad 4, Nos. 13, 15 and 16, were negative in the first and second cultures; positive in the third and fourth cultures. No. 14 was positive in the first and third cultures, negative in the second, absent for the fourth culture.

This experiment was unsatisfactory. Eight men failed to appear for the fourth culture and could not be obtained later. The treatment was changed. On the whole, it led us to doubt the efficacy of dichloramin-T dissolved in chlorcosane.

EXPERIMENT 6.—Phenol, 3 per cent., in glycerin. Treatment given as in Experiment 3. Results are shown in Table 5. All these carriers were of Type IV and all positives later showed the same type. The results suggest that phenolized glycerin is slightly less efficacious than phenolized oil.

EXPERIMENT 7.—Quinin sulphate in 2 per cent. solution with a few drops of aromatic sulphuric acid. Applied as a spray in each nostril for fifteen seconds and in the throat thirty seconds for each treatment. Begun April 3, 1918, ended April 18, 1918.

Squad 1, treated once daily; Squad 2, treated twice daily; Squad 3, treated three times daily; Squad 4, treated four times daily. Cultures were made on the fourth, seventh, tenth, twelfth, fourteenth and sixteenth days.

Results: First culture, two positive; second culture, eight positive; third culture, four positive; fourth culture, eight positive; fifth culture, two positive; sixth culture, four positive.

Carrier 10 was reported as Type III on the second culture. All other positives were Type IV. All were originally Type IV.

We endeavored to obtain optochin for this experiment but were unable to do so. The sulphate of quinin seems of little value.

EXPERIMENT 8.—Eucalyptol from April 3, 1918, to April 8, 1918, inclusive. Dobell's solution from April 9, 1918, to April 11, 1918, inclusive. Chlorcosane from April 12, 1918, to April 17, 1918, inclusive.

No very definite results could be drawn from this experiment; the results were poor.

EXPERIMENT 9.—Chloramin-T sprayed into nostrils and throat. The treatments were given from one to four times daily. Cultures were made on the fourth, seventh, tenth, twelfth and fourteenth days. Results: First culture, one positive; second culture, five positive; third culture, seven positive; fourth culture, ten positive, two absent; fifth culture, four positive, three negative. Twelve of these men developed influenza and were transferred to the wards. A distinct tendency to somnolence was noted in the men receiving the larger number of doses daily. Chloramin-T was regarded as inefficient.

TABLE 5.—RESULTS IN EXPERIMENT 6

	Day																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
No. 1	1	1	1	0	1	1	0	1	1	+	1	1	0	..	..	..	..	..
No. 2	1	1	1	0	1	1	0	1	1	0	1	1	..	..	..	..	..	..
No. 3	1	1	1	0	1	1	0	1	1	0	1	1	0	..	..	..	..	..
No. 4	1	1	1	0	1	1	0	1	1	0	1	1	0	..	..	..	..	..
No. 5	2	2	2	0	2	2	+	2	2	0	2	2	+	2	2	0	2	0
No. 6	2	2	2	0	2	2	0	2	2	0	2	2	0	..	..	..	..	..
No. 7	2	2	2	+	2	2	0	2	2	0	2	2	0	..	0	..	..	0
No. 8	2	2	2	0	2	2	0	2	2	0	2	2	0	..	..	..	..	..
No. 9	3	3	3	0	3	3	0	3	3	..	3	3	..	..	..	..	..	..
No. 10	3	3	3	0	3	3	0	3	3	+	3	3	+	3	3	0	3	..
No. 11	3	3	3	+	3	3	0	3	3	0	3	3	0	3	3	+	3	0
No. 12	3	3	3	0	3	3	+	3	3	+	3	3	0	3	3	+	3	0
No. 13	4	4	4	0	4	4	+	4	4	+	4	4	0	4	4	+	4	0
No. 14	4	4	4	0	4	4	+	4	4	0	4	4	0	4	4	0	4	..
No. 15	4	4	4	0	4	4	0	4	4	0	4	4	..	..	..	..	..	..
No. 16	4	4	4	0	4	4	0	4	4	0	4	4	0	..	..	..	..	..

Figures indicate number of treatments daily. Plus sign indicates a positive culture, minus sign a negative culture. Blank space indicates that man was absent.

EXPERIMENT 10.—Two per cent. dichloramin-T in chlorcosane. Sixteen men in four squads. Used as spray as in former experiments.

Squad 1, one treatment daily; Squad 2, two treatments daily; Squad 3, three treatments daily; Squad 4, four treatments daily. Cultured on the fourth, sixth and eighth days: First culture, three positive, twelve negative, one absent; second culture, none positive, thirteen negative, three absent; third culture, three positive, ten negative, three absent. All the positive cultures were Type IV. This is an unsatisfactory experiment, but may be regarded as tending to the belief that the solution has some effect on the pneumococcus.

As we were particularly anxious to determine the value of dichloramin-T the preceding experiment was twice repeated under identical conditions.

EXPERIMENT 11.—Two per cent. dichloramin-T in chlorcosane. First culture, six positive, five negative, five absent; second culture, eight positive, three negative, five absent; third culture, five positive, six negative, five absent.

EXPERIMENT 12.—Two per cent. dichloramin-T in chlorcosane. First culture, five positive, eight negative, three absent; second culture, six positive, seven negative, three absent; third culture, three positive, ten negative, three absent. These experiments tend to throw doubt on the efficacy of dichloramin-T in chlorcosane. The cases not tested all remained positive.

SUMMARY

The results of the disinfection experiments may be summarized as follows:

1. Dichloramin-T dissolved in eucalyptol gave good results. Used in solution in chlorcosane the results were far less satisfactory.

2. Chlorin gas is not efficient and caused discomfort and is possibly dangerous even in such concentration as was used.

3. Phenol as used shows good results. The solution in oil is more efficacious than that in glycerin. The use of instillations rather than sprays is perhaps preferable on account of reduced danger of ear infection.

4. Iodin in oil gave good results. It is usually available and caused no discomfort.

5. Quinin sulphate proved of no value against the pneumococcus. An accidental observation suggests that it may be valuable in another way. The experiment was under way when the spring epidemic of influenza visited the camp. The carriers of other groups were attacked by the disease in the same proportion as the men of the rest of the camp. No cases of the disease developed in the group being sprayed with the quinin. The prompt subsidence of the epidemic prevented further observations.

6. Chloramin-T is apparently of little value.

While many factors beyond our control have combined to make much of this work unsatisfactory we feel that we are justified in advancing the following conclusions and suggestions as least tentatively.

CONCLUSIONS

1. We have at our command a technic for the detection of carriers of the pneumococcus that is simple, accurate, practical for use on large numbers of men, and open to no more objection than the methods employed so largely in the meningococcus carrier work.

2. The application of this method to 700 men showed the presence of 16 per cent. of carriers of the pneumococcus. Twenty-five per cent. of these carriers harbored organisms of the so-called fixed types. According to the figures given by Cecil and Vaughan for the pneumonia occurring in the same camp during the latter half of the same year in which these studies were made, the percentage of pneumococcus pneumonia due to organisms of the fixed types was 18.6. As this included the period of the great influenza epidemic when Type IV infections were usually prevalent, it will be seen that the proportion of fixed types among carriers and among cases is not far from the same.

3. The tent survey reported above strongly supports the idea that carriers are an important factor in the spread of pneumonia.

4. Owing to the diversity of the Type IV group as at present understood, specific vaccination against it is not practicable. In the cantonments during the war, however, this group of pneumococci has been responsible for more fatalities, and for far more disability than the organisms of the fixed types. Hence we feel justified in advocating disinfection methods directed against carriers.

5. The oily solutions of phenol and of iodin have proven most valuable in our hands for this purpose. They are usually available and easily and safely applied by untrained men.

6. We believe that the contacts of cases of pneumonia should be subjected to culture in the same way as is now done for contacts of meningitis. That when such contacts are shown to be carriers of the same type of pneumococcus as that infecting the patient, vigorous antiseptic treatment should be instituted, combined with such measure of isolation as conditions permit.

7. We wish to advance the opinion that in the presence of epidemics of pneumonia or of diseases fatally complicated thereby such as influenza or measles, it is practical to treat large numbers of men by these methods, and that such treatment should result favorably.

ANTIPYRETICS. I. THE BENEDICT RESPIRATION CHAMBER AT THE NEW HAVEN HOSPITAL

HENRY G. BARBOUR, M.D.
NEW HAVEN, CONN.

Comprehensive studies of antipyretic substances have not been made in recent years. While many questions bearing on relative superiority and manner of employment still require attention, the most inviting problem is, perhaps, the fundamental one of modus operandi. Researches in this direction should broaden our understanding of fever.

This series of papers on antipyretics will deal especially with clinical investigations of the respiratory exchange. This method of attack throws light from two important angles, the behavior of the heat balance and the nature of the materials burned.

The older antipyretics were, in their day, submitted to extensive investigation,[1] chiefly by the method of direct calorimetry. Although quantitative determinations of heat production and elimination were made, attention was not directed toward the respiratory quotient; nothing, therefore, is known of the relation of antipyretic action to the nature of the combustions. In this connection, the carbohydrate metabolism is of special interest in view of recent demonstrations of the influence on heat regulation which may be exerted by dextrose.[2]

For the purpose of studying the respiratory exchange as influenced by antipyretic substances, particularly in disease, I have installed at the New Haven Hospital a Benedict respiration chamber. This cot chamber, on account of its comparative simplicity and the comfort experienced by the subject, affords the most advantageous method of determining the respiratory exchange in the clinic. As is well known, it can be used in many pathologic cases in which mask and mouthpiece

*From the Department of Pharmacology, Yale University School of Medicine.

*The expenses of this research were defrayed largely from the Francis E. Loomis Research Fund of the Yale University School of Medicine.

1. Ott, I., Modern Antipyretics, Easton, Pa., 1892; Fever, New York, 1914. Loewi, O.: Ergebn. d. Physiol. **3**:332, 1904. Textbooks of Cushny, Sollmann and Meyer-Gottlieb. The earlier calorimetric studies are unsatisfactory because sufficient emphasis has not been laid on the exclusion of muscular activity. Benedict and Homans (1911) introduced the feature of a continuous record of the state of rest or of restlessness of the subject.

2. Barbour, H. G.: Proc. Soc. Exper. Biol. & Med. **16**:136, 1919, and Balcar, J. O., Sansum, W. D., and Woodyatt, R. T.: Fever and the Water Reserve of the body, Arch. Int. Med. **24**:116 (July 15) 1919.

methods are impossible. The use of the chamber in conjunction with the Benedict universal respiration apparatus has been minutely described by Benedict and Tompkins,[3] to whose work reference should be made for the details.

The present report has a twofold purpose: First, to give a general description of the New Haven apparatus, pointing out the respects in which it differs from that described by Benedict and Tompkins; and, secondly, to record the results of certain check experiments. These results will illustrate our methods of calculation, serving especially as an index of the degree of accuracy attainable under our conditions.

THE NEW HAVEN HOSPITAL RESPIRATION CHAMBER

Apparatus for the entire routine, including gas analysis, is conveniently arranged in a room having the dimensions of 19⅓ by 12⅓ feet. The exposure is west, enabling the maintenance of a fairly even room temperature for the experiments, which are conducted as early in the day as feasible. The features which are in any way peculiar to

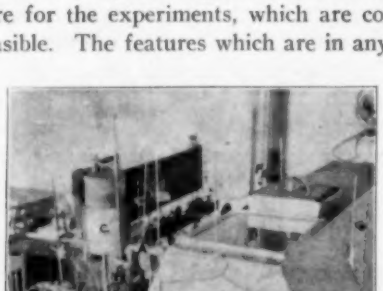


Fig. 1.—New Haven Hospital Respiration Chamber. A, position of "wet bulb" in outflow pipe. B, window. C, spirometer. D, one of the acid bottles in universal respiration apparatus. E, galvanometer. F, oxygen tank. G, fan. H, kymograph.

our apparatus relate chiefly to the size and shape of the chamber, the location of certain of its connections, the cooling system, the graphic records and other accessories.

The chamber (Fig. 1) is constructed of ordinary metal sheeting instead of copper, and presents an angular rather than a curved top. The inside dimensions are: length, 197.8 cm.; width at base, 64.5 cm.; height from constant level of water in water seal, 55.5 cm. The volume of the contained air, when no allowance is made for the spring or other

3. Benedict, F. G., and Tompkins, E. H.: Boston M. & S. J. **174**:857 (June 15) 1916; ibid. **174**:898 (June 22) 1916; ibid. **174**:939 (June 29) 1916.

contents, is approximately 637 liters. The waterseal is constructed from 3 inch gutter secured to a wooden frame, the whole base being supported by an iron pipe frame at a height of 30 inches from the floor. The 2½ liter spirometer which serves as the tension equalizer is connected directly with the chamber by a one-half inch pipe in its base; this pipe also receives the one-eighth inch inlet from the oxygen supply. The latter is admitted through a 1 liter Danish gas meter.[4] The ventilation circuit leads from the universal respiration apparatus to an opening in the base of the chamber at its foot end. It can be seen in the illustration leaving the chamber at the upper left hand corner of the head end, where the "wet" and "dry" bulb thermometers are located. The samples of chamber air which are analyzed for "residual carbon dioxid" are taken from below, through an opening in the center of the chamber base.

Fig. 2.—Chamber without cover. A, signal button. B, bulb for transmitting muscular movements to recording tambour. C, gutter serving as water seal. D, stethoscope. E, shelf for gas sampling apparatus.

The cooling system includes not only a high speed fan, but also a thin flannel blanket for summer work which closely fits the entire chamber top, and is wet thoroughly as soon as the chamber is closed at the begnning of an experiment. It is kept cool by a sprinkling device consisting of a pail of ice water which drains into a quarter inch pipe running a few inches above the chamber for its entire length. This pipe is perforated at suitable intervals and is provided with two

4. This meter has been calibrated with weighed oxygen of known purity according to the method of F. G. Benedict: Physical Rev. **22**:294, 1906. Our correction factor is 1.009.

cross branches at the head of the chamber. With this arrangement the average temperature is easily kept at a level no higher than from 23 to 24 C. in the hottest weather.

Besides the graphic records of muscular activity of the subject and of the time and "awake" signals, there is kept synchronously on the kymograph a tracing of the movements of the spirometer. This last serves as a check on the calculation of the admission of oxygen when necessary, and is also convenient in presenting at a glance either sudden or gradual changes in the chamber temperature.

Other accessories are the 2-inch Bowles' stethoscope, kept secured to the subject's chest, by which the pulse rate and the electric thermocouples for the rectal temperature are followed. The thermocouples consist of copper—constantan (No. 25 gage) junctions; one of which is kept at a distance of about 10 cm. within the rectum; the other in a Dewar flask outside the chamber. A Leeds and Northrup portable mirror galvanometer (No. 2,400 A) is used. As now installed, 8.8 units on the scale correspond to 1 C. At the beginning and close of every experiment with a subject the galvanometer readings are checked by a mercurial thermometer.

CHECK EXPERIMENTS

Alcohol[5] check experiments are made at frequent intervals to demonstrate that the chamber remains air-tight. The results of two such experiments are presenteed in Tables 1 and 2.

TABLE 1.—ALCOHOL CHECK EXPERIMENT MADE MAY 1, 1919, TO DEMONSTRATE THAT THE CHAMBER REMAINS AIRTIGHT

Period	Duration in Minutes	Residual Carbon Dioxid	Liters Carbon Dioxid			Carbon Dioxid, C.c. per Minute	Liters Oxygen				Oxygen, C.c. per Minute	Respiratory Quotient
			Difference	Absorbed by Soda Lime	Produced		Oxygen plus Nitrogen	Difference	Admitted	Consumed		
B	..	2.49	.....	....	....	.....	582.15					
P	47	1.77	—0.72	8.40	7.68	163.42	585.29	+3.14	15.20	12.06	256.60	0.64
I	30	2.02	+0.25	4.84	5.09	169.67	584.89	—0.40	7.13	7.53	251.10	0.68
II	32	1.77	—0.25	5.10	4.85	151.56	585.09	+0.80	8.08	7.28	227.56	0.67
III	37	1.78	+0.01	5.83	5.84	157.84	585.37	—0.32	8.81	9.13	246.76	0.64
IV	29	1.77	—0.01	4.50	4.49	154.83	585.09	—0.28	6.46	6.74	232.41	0.67
V	30	1.71	—0.06	4.67	4.61	153.67	585.95	+0.86	7.53	6.67	222.33	0.69
VI	31	1.54	—0.17	4.69	4.52	145.16	585.32	—0.63	6.14	6.77	218.39	0.68
VII	25	1.65	+0.11	5.09	5.20	148.57	583.78	—1.54	6.47	8.01	228.86	0.65
VIII	28	1.54	—0.11	4.04	3.93	140.36	584.17	+0.39	6.19	5.80	207.14	0.68
Total	290	....	.....	....	46.21	154.55*	.....	.....	....	69.99	234.08*	0.66*

* Average.

5. The theoretical respiratory quotient for alcohol is 0.667. The slightest leak in the closed system causes the carbon dioxid and oxygen determinations to vary from the true figures in opposite directions, thus making an appreciable error in the respiratory quotient.

In addition, the respiratory quotients for periods of ninety-four minutes or less, given in Table 3, have been obtained.

These alcohol checks show that the theoretical respiratory quotient for alcohol is attainable when the apparatus is operated continuously for a number of half-hour periods. In the two cases detailed in Tables 1 and 2, the preliminary periods (P) afforded satisfactory respiratory quotients; but since it may require some time for the temperature of the chamber to become stabilized, we never rely on the oxygen figure for the preliminary period. After the ventilation system has been running for thirty minutes, however, satisfactory respiratory quotients (maximum variation ± 0.03 can be obtained for each individual half-hour period.

TABLE 2.—ALCOHOL CHECK EXPERIMENT MADE JUNE 30, 1919, TO DEMONSTRATE THAT THE CHAMBER REMAINS AIRTIGHT

Period		Duration in Minutes	Carbon Dioxid, C.c. per Minute	Oxygen, C.c. per Minute	Respiratory Quotient
10:16½	P	23½	259.70	372.54	0.697
10:40¾	I	33¼	256.24	399.10	0.642
11:24½	II	34⅝	247.22	376.97	0.662
12:00⅝	III	36¼	233.93	335.72	0.697
I–III		104¼	245.46*	368.63*	0.666*

* Average.

TABLE 3.—RESPIRATORY QUOTIENTS

Date	Duration of Preliminary Period, Minutes	Duration of Calculated Period, Minutes	Respiratory Quotient
Feb. 3, 1919	21	62	0.670
May 7, 1919	30	90	0.665
June 9, 1919	36	94	0.665
June 17, 1919	30	92	0.659

TABLE 4.—RESULTS OF OBSERVATIONS MADE ON A NORMAL INDIVIDUAL (W. J. C.); WEIGHT, 81.1 KILOGRAMS; SURFACE AREA, 2.02 SQUARE METERS (EXPERIMENT OF APRIL 1, 1919)

Time	Duration	Liters		Respiratory Quotient	Per Minute				Per Square Meter per Hour	
		CO_2 Produced	O_2 Consumed		CO_2 C.c.	O_2, C.c.	Calories Produced	Calories Eliminated	Calories Produced	Calories Eliminated
2:55 (P)										
3:25 (I)	30	6.86	8.08	0.85	229	269	1.30	....	38.6	
3:55 (II)	30	7.10	8.25	0.86	237	275	1.34	....	39.8	
4:28 (III)	33	7.67	8.84	0.88	232	265	1.32	....	39.2	
Total	93	21.63	25.17	0.86*	233*	271*	1.32*	1.32*	39.2*	35.9*

* Average for three periods.

Calculation of an Experiment with a Human Subject.—The data presented in Table 4 will serve to illustrate the use of the apparatus with a normal human subject.

It will be seen that the half-hour figures for the respiratory quotient stand in excellent agreement. Since the half-hour oxygen data were, especially in the earlier months of our experience, usually more at variance than in this experiment, we have been accustomed, up to the present time, to calculate the heat production in calories from the half-hour carbon dioxid determinations. The calory factor employed is the one which corresponds to the average respiratory quotient for the day, i. e., ninety or more minutes. In the experiment outlined in Table 4, for example, the average respiratory quotient for the three periods was 0.86, for which the calory factor is 5.669. Multiplying each carbon dioxid determination by this factor one obtains, respectively, 1.30, 1.34 and 1.32 calories per minute. For a surface area of 2.02 square meters (Dubois linear formula) this gives, respectively, 38.6, 39.8 and 39.2 calories per square meter per hour, or an average of 39.2 calories for the whole experiment.

When the method of indirect calorimetry is employed, heat elimination can be determined only by following the average body temperature. The rectal temperature, although it gives under ordinary conditions an absolute value which is something like 0.5 C. too high,[6] affords a fair criterion when employed only for differential purposes, i. e., to determine the *changes* in average body temperature. In the experiment of April 1, 1919, the rectal temperature curve showed a net change of + 0.14 degrees during the ninety-three minutes. The subject weighing 81.1 kilograms and having a thermal equivalent of 67.3 (81.1 × 0.83), therefore stored 9.42 (67.3 × 0.14) calories during this time. This gives an average accumulation of 0.10 calories per minute, which, subtracted from a heat production of 1.32 calories, gives a total elimination of 1.22 calories per minute, or 35.9 calories per square meter per hour.

CONCLUSIONS

The Benedict respiration chamber appears admirably adapted to clinical studies of the respiratory exchange. After the ventilation circuit has been run for a preliminary period of thirty minutes, half-hour periods are of sufficient length for following the heat balance. The respiratory quotient can, within ninety minutes, be determined with a high degree of accuracy. For the individual half-hour periods, the variation in the respiratory quotient need not be over ± 0.03.

The procedure is certainly well tolerated in every way by many patients on whom investigations by mask or mouthpiece methods would be impracticable.

6. Barr, D. P., and DuBois, E. F.: Clinical Calorimetry, Arch. Int. Med. **21**:627 (May) 1918.

ANTIPYRETICS. II. ACETYLSALICYLIC ACID AND HEAT REGULATION IN NORMAL INDIVIDUALS *

HENRY G. BARBOUR, M.D., AND MICHAEL M. DEVENIS, M.D.

NEW HAVEN, CONN.

Acetyl salicylic acid (aspirin), introduced into therapeutics by Dreser,[1] is today the most widely used of antipyretic drugs. Its action on the heat regulating mechanism has, however, been subjected but little to careful investigation. That other salicylates possess antipyretic and analgesic properties of a feebler order than those of acetylsalicylic acid was emphasized by the work of Bondi and Katz,[2] who associated the difference with the fact that the acetyl ester appears to be absorbed and distributed largely intact, salicylate being but slowly split off in the intestine.

The effects of this substance on the heat regulation of normal and of febrile human subjects, respectively, will be dealt with here and in the third paper of the series. Essentially, they are studies of the respiratory exchange in correlation with the body temperature.

LITERATURE OF SALICYLATES IN RELATION TO HEAT REGULATION

Buss[3] investigated the effects of sodium salicylate on the carbon dioxid production both of normal subjects and of patients with typhoid, tuberculosis and diphtheria. This was done with the Liebermeister apparatus, which from the present day standpoint can scarcely be regarded as adapted to the making of accurate determinations. Furthermore, the preparation employed by this author appears to have contained a high percentage of sodium cresotinate, a substance which appears to possess similar properties.

Buss found that sodium salicylate (in doses of from 6 to 8 gm.) produced in his fever patients no reduction of the carbon dioxid output in spite of reductions in temperature of several degrees centigrade. There was often in fact an increase in the carbon dioxid after an hour or more had elapsed. He states that similar doses in normal individuals give no diminution in the carbon dioxid production, but it does not appear whether or not these cases may have exhibited an increased output.

---

* From the Department of Pharmacology, Yale University School of Medicine.

* The expenses of this research were defrayed largely from the Francis E. Loomis Research Fund of the Yale University School of Medicine. A preliminary report appears in the Proceedings of the Society for Pharmacology and Experimental Therapeutics, J. Pharmacol. & Exper. Ther. **13**:499 (Aug.) 1919.

1. Dreser, H.: Pflüger's Arch. **76**:306, 1899.
2. Bondi, S. & Katz, H.: Ztschr. f. klin. Med. **72**:177, 1911.
3. Buss, C. E.: "Ueber Wesen und Behandlung des Fiebers," Stuttgart, 1878.

Livon[4] found with one exception a decided increase in the carbon dioxid production in experiments on guinea-pigs, turtles and frogs with sodium salicylate.

Wood and Reichert[5] gave from 1 to 5 gm. doses of sodium salicylate to normal dogs. A 43.3 per cent. increase in heat dissipation was calculated by means of a water calorimeter. This was associated with an increase of 39.6 per cent. in the heat production.

Stuehlinger[6] studied the action of sodium salicylate on normal guinea-pigs in a Rubner calorimeter. The effects on body temperature were variable. Five of the six experiments showed changes in the heat production varying from a 4 per cent. loss to a 10 per cent. gain. The other case showed an 82 per cent. gain. The heat dissipation was in every case increased, the change varying from 2 to 4 per cent. above normal, except in one case showing a 59 per cent. increase.

Apparently the only modern studies of sodium salicylate on the respiratory exchange are those of Denis and Means,[7] who studied three men from the surgical wards of the Massachusetts General Hospital. Benedict's universal respiration apparatus with spirometer and mouth piece were used. Observations were made with the subjects in a fasting condition and at complete rest. Each day's experiment consisted of three ten minute periods. Subject 1, aged 28 years, after receiving 15.45 gm. sodium salicylate over a period of three days, exhibited a rise of 15 per cent. above the basal metabolism (mild salicylism noted). Subject 2, aged 41 years, was described as mildly septic and apparently had a high basal metabolism at the beginning. There was no change noted after 23.45 gm. sodium salicylate had been administered over a period of four days. Subject 3, aged 64 years, took 19.2 gm. sodium salicylate over a period of three days without altering his basal metabolism. The respiratory quotations were not altered by the drug.

To summarize the results of these investigations on sodium salicylate, it may be said that after rather large doses, evidence of an increase in the heat production has been found frequently but not constantly in normal animals and man. No conclusion can be reached as to the effects of sodium salicylate on the total metabolism of the febrile organism.

The effects of acetylsalicylic acid on the energy exchange have apparently never been submitted to serious investigation. A careful search for literature bearing on this point has brought to light only the three rabbit experiments of Singer.[8] This author determined the oxygen consumption in normal animals, employing a Regnault-Reiset apparatus. Two rabbits received each 0.3 gm. acetyl salicylic acid *per os* and exhibited decreases in the oxygen consumption of 17 and 14 per cent. respectively; a "toxic" dose, 0.9 gm. in the third animal, was followed by a 9 per cent. increase.

PRESENT WORK

Subjects.—Five normal individuals served as subjects, including three medical students besides the authors. Descriptive data are given in Table 1.

Apparatus.—The Benedict respiration chamber and other apparatus employed have been described in the first paper of this series.[9]

4. Livon, Ch.: Compt. rend. Acad. d. sc. **90**:321, 1880.
5. Wood and Reichert: J. Physiol. **3**:321, 1882.
6. Stuehlinger: Arch. f. exper. Path. u. Pharmacol. **43**:166, 1900.
7. Denis, W., and Means, J. H.: J. Pharmacol. & Exper. Therap. **9**:273, 1916.
8. Singer, H.: Pflüger's Arch. **84**:527, 1901.
9. Barbour, H. G.: Arch. Int. Med., this issue, p. 611.

Procedure.—Owing to other engagements of the subjects, it was not feasible to conduct this series of experiments in the morning. A very light breakfast was therefore allowed at least six hours previous to the beginning of the experimental period. The breakfast did not include meat or eggs, and was always identical in the case of two or more experiments on the same individual.

TABLE 1.—Data on Experiment Subjects

Subject	Age, Years	Weight, Kg.	Surface Area, Square Meters (Dubois' Linear Formula)	Acetylsalicylic Acid, Gm.
H. G. B.	33	64.6	1.76	1.0
M. M. D.	27	50.8	1.60	1.0
W. Y. S.	28	71.1	1.84	1.0
W. J. C.	31	81.1	2.02	1.25
H. J. S.	33	68.9	1.81	1.0

The subject lay down on the cot fifteen minutes before the cover was put in place. During this period the stethoscope and rectal thermocouple were adjusted and preliminary readings taken of pulse and body temperature. The latter reading at the beginning and end of each day's work was controlled by a mercurial thermometer.

One or 1.25 gm. acetylsalicylic acid were given by mouth with 250 c.c. water. The drug was given sometimes before closure of the chamber, but more often toward the end of the "preliminary period." In the control experiments the same amount of water was given without the drug. In two of the experiments reported here, control periods were run on the same day and previous to the drug experiment. This procedure was ultimately abandoned, being too tedious for the subject.

As soon as the cover was lowered the air mixer within the chamber was started; at the end of fifteen minutes the ventilation circuit was turned on, enough carbon dioxid having accumulated by this time to furnish a fairly constant residual level. A preliminary period of from 30 to 45 minutes followed before the beginning of the experimental period proper, from which the results are reported. The latter period lasted from one and one half to two hours. This was divided approximately into half-hour periods, the change between periods always being deferred when necessary to a moment when the chamber temperature was exhibiting little or no fluctuation. All of the determinations of chamber temperature, barometric pressure, body temperature, pulse, etc., were made as nearly as possible at the moment when one period closed and the next began. The samples of chamber air for the residual carbon dioxid were, of course, taken at this time also.

The results were all calculated as described in Paper I.

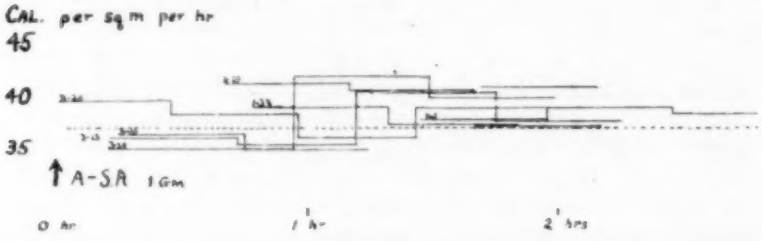
RESULTS

The results of six control experiments and five experiments with acetylsalicylic acid are tabulated in Table 2. Attention may be called to the following points:

Carbon Dioxid Production.—It will be seen that this was definitely higher after the drug had been taken in the case of four out of the five individuals, the first exhibiting practically no difference.

Oxygen Consumption.—The oxygen consumption changes are similar, showing that therapeutic doses of acetyl salicylic acid in normal individuals exhibit in the majority of cases a mild stimulation of the total metabolism.

Respiratory Quotient.—Since the respiratory quotients given represent a period of one and one-half or more hours' continuous experimentation, they may be regarded as sufficiently accurate for the calculation of the heat production in calories. There is probably no change in the nature of the materials burned, for the results as a whole indicate that the drug, in this dosage, does not alter the respiratory quotient of normal persons.



Heat production in calories per square meter per hour. Broken line: Average normal level for the five subjects. Unbroken line: Determinations following ingestion of acetylsalicylic acid, given at the zero hour. Date of each experiment (Table 2) noted at its initial point.

Heat Production.—When expressed as calories per square meter per hour (by calculation from the respiratory quotient for the day), it will be seen that the average increase in heat production for the entire series of drug experiments amounted to 6.1 per cent. above normal. The change is best shown in the diagram, where each experiment is plotted in the proper time relation to the arrow representing drug administration. The broken line indicates the average level of heat production for the same individuals without the drug.

During absorption of the drug the figures are grouped around the normal level. The maximal effect appears during the fourth half hour after administration, at which time the heat production is above normal

TABLE 2.—Results of Administration of Acetylsalicylic Acid to Normal Subjects

Subject	Date	c.c. per Minute				Respiratory Quotient	Per Square Meter per Hour				Body Temperature		Pulse Rate	
		Carbon Dioxid Production		Oxygen Absorption			Calories Produced		Calories Eliminated					
		Control	Acetylsalicylic Acid	Control	Acetylsalicylic Acid		Control	Acetylsalicylic Acid	Control	Acetylsalicylic Acid	Change, C.	Initial, C.	Change per Min.	Initial per Min.
H. G. B.	3–27	205	...	246	...	0.84	40.4	....	42.3	....	−0.13	37.46	−8	68
	4–9	...	203	...	243	0.83	....	40.2	....	41.9	−0.08	36.98	+2	64
M. M. D.	2–20	179	183	...	226	0.81	37.7	38.7	36.7	39.0	+0.02, −0.02	36.65	+4, −4	68
W. Y. S.	1–23	203	237	...	...	0.89	36.5	42.6	42.7	38.0	−0.30, +0.22	36.67		
W. J. C.	4–1	...	233	...	271	0.86	....	39.2	....	35.9	+0.15	36.60	−4	72
	4–3	218	...	247	...	0 88	36.1	....	37.2	....	−0.05	36.59	−8	80
H. J. S.	3–24	...	213	...	243	0.87	....	40.6	....	41.9	−0.13	37.04	−9	63
	4–15	207	...	238	...	0.87	38.4	....	39.2	....	−0.04	36.83	0	54
Average	....	....	....	....	....	....	....	37.82	40.28	39.62	39.24				
Change	....	....	....	....	....	....	....	....	+6.1%	....	−0.7%				

in all seven cases. (Two cases plotted are not included in Table 2 because of the factor of sleep.)

Heat Elimination.—As explained in the first paper of this series, heat elimination was calculated on the assumption that changes in the rectal temperature run parallel to changes in average body temperature. On this basis there was found in the entire series no significant difference in the heat elimination betweenn normal and drug experiments; in the latter case it was 0.7 per cent. less than in the former.

Body Temperature.—The failure of the heat elimination to increase proportionately to heat production is associated with a relatively slight increase in the body temperature. The table shows that there was a tendency for the body temperature to fall somewhat (average, — 0.08 C.) during the experimental period when no drug was given. The acetylsalicylic acid, by increasing the heat production, overcompensated for this fall, but never raised the body temperature more than 0.22 C. above the starting point, the average increase being + 0.03 C. The initial body temperature for each experiment is presented in the second temperature column.

Pulse Rate.—The last two columns show that acetylsalicylic acid exerts no constant effects on the slow pulse of a normal individual at complete muscular rest in a nearly fasting condition.

SLEEP EXPERIMENTS

In two additional experiments the subject was allowed to sleep as long as possible; in each case this amounted to about one hour. The details are as follows:

EXPERIMENT OF MARCH 10, 1919.—H. G. B. took 1 gm. acetylsalicylic acid at 2:10 p. m.—in this case near close of preliminary period. He slept from 3 to 4 p. m. During the period from 2:25 to 4:25 p. m., the average carbon dioxid production was 197 c.c. per minute, the average oxygen consumption 222 c.c. per minute, giving a respiratory quotient of 0.89. Heat production and elimination were respectively 38.2 and 35.7 calories per square meter per hour. Temperature at 2:30 p. m. was 37.2 C.; at 3:25 p. m., 37.1 C.; at 4:25 p. m., 37.35 C.

Calory production by half-hour periods (Fig. 1): 37.2; 35.8; 41.2; 38.4.

EXPERIMENT OF MARCH 13, 1919.—M. M. D. took 1 gm. acetylsalicylic acid at 2:55 p. m., during the end of the first period. He slept from 3:28 to 4:18 p. m. From 2:55 to 5:04 p. m. the average carbon dioxid production was 179 c.c. per minute, average oxygen consumption 216 c.c. Respiratory quotient, 0.83. Average heat production and elimination, respectively, 38.3 calories and 41.7 calories per square meter per hour. The body temperature at 2:55 p. m. was 36.75 C.; at 5:05 p. m. it was 36.5 C.

Calory production by half-hour periods (Fig. 1): 36.9; 36.2; 41.3.

Notwithstanding the practically perfect freedom from activity achieved, it will be seen that in both experiments a much higher level of heat production was attained in the second than in the first hour

after taking the drug. The best evidence of its stimulating effect on the metabolism is thus afforded.

Does Sleep Favor the Exhibition of Antipyretic Action?—One purpose of these two experiments was to determine whether a condition of narcosis would have any influence in bringing to light the antipyretic action of acetylsalicylic acid which is otherwise not exhibited in normal individuals. Had an affirmative result been reached, an analogy might have been drawn between sleep and fever.

Since no significant temperature depression could be elicited under these conditions, we concluded that sleep does not favor the exhibition of antipyretic action by the drug.[10] Sensitivity to antipyretics probably depends therefore on something different from central depression. This militates against the theory that antipyretic action is a manifestation of central stimulation. (See following paper.)

CONCLUSIONS

1. Normal individuals usually respond to acetylsalicylic acid (1 gm. per os) by an increase in the carbon dioxid output and heat production. The maximum effect is reached during the fourth half hour after administration.

2. The average heat production of five subjects was 40.3 calories per square meter per hour after taking the drug, as against the basal average, for these persons, of 37.8 calories; an increase of 6.1 per cent. was thus indicated.

3. In spite of the increased metabolism, heat dissipation was not significantly altered.

4. During the control experiments the average change in body temperature was — 0.08 C.; after the drug it was + 0.03 C.

5. The respiratory quotient does not appear to be altered by the drug in normal individuals. The same is true of the pulse rate.

6. Sleep does not appear to favor the exhibition of antipyretic action by acetylsalicylic acid.

The authors take pleasure in acknowledging with thanks the very helpful coöperation of Messrs. W. J. Craig, W. V. Sayad and H. J. Stander, who acted as subjects in some of the experiments.

10. The state of sleep has, if anything, tended to bring out the stimulating effect of the drug on heat production. (See third period of each experiment.) Cf. effect of antipyrin and of sodium salicylate on decerebrate animals as described by Barbour and Deming, J. Pharmacol. & Exper. Therap. **5**:149, 1913, and by Isenschmid, Arch. exper. Path u. Pharmakol. **75**:10, 1913.

ANTIPYRETICS. III. ACETYLSALICYLIC ACID AND HEAT REGULATION IN FEVER CASES*

HENRY G. BARBOUR, M.D.

NEW HAVEN, CONN.

In the foregoing paper[1] it has been shown that acetylsalicylic acid, in 1 gm. doses, has but a slight effect on the heat balance of normal individuals. An average increase of 6.1 per cent. above the normal heat production was obtained in five cases, the maximum effect occurring during the fourth half hour after giving the drug by mouth. A very slight tendency to raise the body temperature was observed. In this paper will be reported the effects of acetylsalicylic acid given in the same amounts in fever cases. As will be seen from the data, during febrile and afebrile phases, as well as in the first stages of convalescence, similar phenomena have been manifested.

In determining the means by which a substance exerts its antipyretic action, it is necessary to know how the energy exchange is affected. Is the reduction in temperature due to an increase in heat elimination or to a decrease in heat production, or are both of these factors concerned in its action?

LITERATURE

As will be seen from the preceding paper, no calorimetric work has been done on acetylsalicylic acid in fever. This is somewhat surprising in view of its alleged superiority[2] as an antipyretic to other salicylates. Sodium salicylate was investigated by Buss,[3] using primitive methods, in cases of typhoid, tuberculosis and diphtheria. His conclusion was that this substance produces no reduction in the carbon dioxid output in fever. At the present time it is generally assumed that salicylates exert antitpyretic action merely by increasing the heat elimination, as do the members of the antipyrin group.

---

* From the Department of Pharmacology, Yale University School of Medicine.

* The expenses of this research were defrayed largely from the Francis E. Loomis Research Fund of the Yale Medical School. A preliminary report appears in the Proceedings of the Society for Pharmacology and Experimental Therapeutics, J. Pharmacol. & Exper. Therap. **13**:500 (Aug.) 1919.

1. Barbour, H. G., and Devenis, M. M.: Arch. Int. Med., this issue, p. 617.
2. Bondi, S. & Katz, H., Ztschr. f. klin. Med. **72**:177, 1911.
3. Buss, C. E.: "Ueber Wesen und Behandlung des Fiebers," Stuttgart, 1878, pp. 67-76.

METHOD

The present work has been done with the Benedict respiration chamber at the New Haven Hospital described in the first paper[4] of this series. The data given in Table 1 relate to the five subjects investigated:

TABLE 1.—DATA ON SUBJECTS OF EXPERIMENT

Subject	Age, Years	Weight, Kg.	Surface Area, Square Meters (Dubois Linear Formula)	Acetylsalicylic Acid, Gm.	Diagnosis	Illness Began
J. D.	25	52.21	1.50	1.0	Tuberculosis (cold abscess)	11/24/18
G. G.	30	49.94	1.54	1.0	Tuberculosis (kidney)	3/21/19
G. M.	14	26.55	1.21	0.75	Osteomyelitis (convalescent)	12/ 6/18
T. W.	47	46.21	1.56	1.0	Pneumococcus empyema (convalescent)	1/16/19
S. L.*	28	55.21	1.63†	1.0	Acute pulmonary tuberculosis	7/12/19

* S. L. received no breakfast. † Dubois' height-weight formula.

Procedure.—The same procedure was employed as described in the second paper[5] with the exception that the experiments were performed in the morning, preceded by three hours by the small breakfast suggested by Soderstrom, Barr and DuBois.[6]

The results divide themselves into a larger group, relating to the effects of acetylsalicylic acid during the exhibition of its antipyretic action and a group of two experiments which illustrate the conditions prevailing during the reaction toward the initial temperature.

The results in the first group, with one exception, appear in Table 2, which includes a control experiment on each of four individuals and six drug experiments on the same group.

Temperature Changes.—The changes in body temperature noted in the table occurred in each case during the exact period for which the metabolism results are reported. It will be seen that on the days on which no drug was given there was a rise in temperature in three out of four cases, the fourth case exhibiting a slight fall. After acetylsalicylic acid, however, a marked temperature fall was observed in every case. This averaged more than 0.8 C. in ninety minutes for the series.

It will be noted that this fall took place in spite of the fact that the initial temperatures were usually but slightly elevated and in some cases were normal. It should therefore be said of antipyretic drugs not that they reduce only an elevated temperature, but that they *reduce*

4. Barbour, H. G.: Arch. Int. Med., this issue, p. 611.
5. Barbour and Devenis, Arch. Int. Med., loc. cit.
6. Soderstrom, G. F., Barr, D. P. and Dubois, E. F.: Arch. Int. Med. **21**: 613 (May) 1918.

the temperature in *fever cases,* afebrile stages and a part of the convalescence period being included.

Carbon Dioxid Production.—When one compares the carbon dioxid production after acetylsalicylic acid with that under the control conditions, the increase exhibited in normal individuals is seen but twice in six cases. The other experiments show a slightly decreased carbon dioxid output, but no more than can be accounted for by the fall in body temperature.

Oxygen Consumption.—The oxygen consumption was increased by the drug in only one case, affording evidence that these doses of acetylsalicylic acid cause, if anything, a diminution in the energy exchange of febrile individuals.

Respiratory Quotient.—It will require a greater number of respiratory quotients than can be reported at present to determine definitely whether acetylsalicylic acid alters the nature of the combustions in febrile cases. Taking the evidence which Table 3 furnishes, together with one case not included therein (because of an unsuccessful control experiment which it was not feasible to repeat), we have an average respiratory quotient of 0.83 for five control experiments, which is increased to an average of 0.87 for seven drug experiments. As this increase appears in four out of five subjects, the tentative suggestion may be allowed that acetylsalicylic acid increases the respiratory quotient in febrile subjects. This increase would indicate that in the metabolic processes of such individuals the drug arouses a more active participation by the carbohydrates. This question is now being investigated in this laboratory from a number of viewpoints.[7]

Heat Production.—When the carbon dioxid production is converted to calories per square meter per hour, the average change in metabolism caused by the drug in this series may be expressed as — 3.5 per cent.

Heat Elimination.—Taking into account the changes in body temperature, the number of calories eliminated have been calculated as explained in Paper I[8] for both of our series of experiments. It will be seen that each individual lost much more heat after the drug than without it. The average heat elimination in the control experiments amounted to 37.7 calories per square meter per hour, while with acetylsalicylic acid, 52.1 calories per square meter per hour were lost by the same subjects, showing an increase of 38.2 per cent. Contrasting this figure with the insignificant change in the heat production, the fact becomes established that this drug exerts its antipyretic action almost entirely by means of an increased dissipation of heat. This

7. Barbour, H. G.: "The Antipyretic Action of Dextrose," Proc. Soc. Exper. Biol. & Med. **16**:136, 1919.

8. Barbour, H. G.: Arch. Int. Med., this issue, p. 611.

has, of course, often been surmised from observation of the marked diaphoresis and increase in surface temperature.

Pulse.—Some diminution in pulse rate was observed in nearly all the experiments. This amounted to an average of one beat per minute for every half hour, in the controls; after taking the drug, however, the difference amounted to 3⅓ beats per minute for each half hour. In one case a temporary disturbance in rhythm occurred and in another (G. M.) a reduction of the rate by nearly one half occurred for a short time, very suggestive of temporary heart block. Certainly one cannot overlook the possibilities of cardiac disturbances resulting from the use of large doses of this drug.

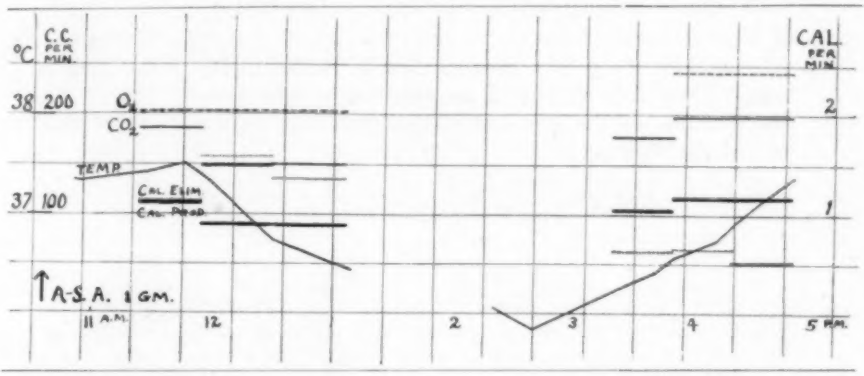


Fig. 1.—Effects of acetylsalicylic acid on J. D. (tuberculous abscess). First half, antipyretic phase; second half, return to initial temperature (another day with essentially the same morning temperature curve).

- - - oxygen, c.c. per minute
—— carbon dioxid, c.c. per minute
/\ body temperature
—— calories produced per minute
.... calories eliminated per minute
Abscissae: hours
Drug administered at arrow both days.

Supplementary to the above results may be mentioned the acetylsalicylic acid experiment on S. L. (July 22, 1919), for which no satisfactory control was obtained. This subject had taken no breakfast at all. The carbon dioxid production and oxygen consumption per minute were respectively 185 and 231 c.c., giving a respiratory quotient of 0.80 and 41.2 (carbon dioxid) calories produced per square meter per hour.

The heat elimination was 45.2 calories per square meter per hour. This figure is sufficiently above all of our control determinations in other subjects to lend support to the conclusion that the drug exerts its antipyretic action by stimulating the heat dissipating process.

The temperature change in this experiment was —0.28 C., the initial temperature of the subject being 37.23 C. The pulse change was —2 beats per minute per half hour.

In Figure 1, is presented graphically the progress by half hour periods of a typical acetylsalicylic acid experiment. The oxygen consumption given (indicated by the dash line), is the average for the entire experiment. The chief diminution in the carbon dioxid output and heat production is seen to take place during the periods of greatest temperature decline. The change in heat production appears slight when compared with the great increase in heat elimination seen during the second period. The maximum effects of the drug appear during the second hour after administration.

Return to Initial Temperature.—This is presented in the last half of Figure 1, taken from the same subject as the first half, but on a different day, the proper time relation to the injection of the drug being maintained. The rectal temperature in this case was followed during the morning and agreed essentially with that shown in the first part of the diagram.

TABLE 2.—Carbon Dioxid Production During Return to Initial Temperature After Taking Acetylsalicylic Acid

Time	Acetylsalicylic Acid, Gm.	Rectal Temperature, C.	Carbon Dioxid Production (C.c. per Minute During Foregoing Period)
9:00 a. m.	...	37.4	
9:15 a. m.	1.0	37.4	
10:00 a. m.	...	37.2	
11:00 a. m.	...	37.2	
12:55 p. m.	...	37.03	
1:55 p. m.	...	36.70	
2:33 p. m.	...	36.91	180.71
3:00 p. m.	...	37.01	193.23
3:30 p. m.	...	37.28	181.48
Average			187.78

It is evident that the return to the initial temperature after acetylsalicylic acid is not associated, as the ascending curve of fever often is, with a marked increase in the heat production; the change is even less than that occurring with the antipyretic effect. Diminution in elimination of heat is the striking feature of the return to initial temperature; this amounted to less than 50 per cent. of the normal figure in the last half hour period shown.

This reaction after antipyretic action was associated with absence of sweating but there was no shivering or sensation of chilliness.

Similar results were noted in an experiment with the subject, G. G. (April 12, 1919). The carbon dioxid production was determined for ninety-nine minutes, beginning with the turning point of the temperature curve. The data shown in Table 2 were obtained.

It will be seen that during the period of reaction from the antipyretic effect, this subject's average carbon dioxid production was slightly lower than on March 5, when no drug was given. Assuming a respiratory quotient of 0.91 (average of this subject's quotients in Table 3) the heat production in this experiment would have been 39.4 calories per square meter per hour, and heat elimination only 30.8 calories. This shows again that the return to initial temperature is accomplished by heat saving rather than by increased heat production.

The results herein reported have shown that acetylsalicylic acid, like other antipyretic drugs, exerts its temperature reducing action essentially by increasing the processes of heat elimination. While stimulation of the metabolism is not seen, as in health, there is at least no depression at all comparable in extent to the increase in heat dissipation.

This action of acetylsalicylic acid is exhibited in afebrile stages and during convalescence, with resulting subnormal temperatures. It is not allowable, therefore, to state that antipyretics reduce an elevated but not a normal temperature; a more correct formulation of the facts is that *antipyretics reduce the body temperature in fever cases* (including temporarily afebrile and convalescent phases) *but not in normal persons.*

SENSITIVITY TO ANTIPYRETIC ACTION

What is the essential cause of this sensitivity to antipyretics on the part of persons who are or have recently been febrile? Its occurrence with normal initial temperatures is fundamentally disturbing to the hypothesis that the febrile state is one of "depression" of the heat regulating mechanism which antipyretics tend to overcome by a "stimulating" action, healthy individuals being, of course, insusceptible to such stimulation. The reinstating of a normal temperature might, it is true, be regarded as a manifestation of stimulation of the heat regulating mechanism, but diversion to a subnormal temperature must be given some other interpretation.

In seeking for a more satisfactory explanation of sensitivity to antipyretics, due consideration must be given to the factor of inanition. This condition is common to fever, afebrile intermissions and convalescence. Is it justifiable to assume that antipyretics will not reduce temperature if a supply of readily combustible material be available? This condition obtains in health but not in inanition, the stores of glycogen having been exhausted. To establish this hypothesis would require the demonstration that antipyretics arouse an excess heat elimination in both health and fever, acting against which a "chemical regulation," e. g., heat production from carbohydrates, would serve to prevent a change in the temperature level. Since, however,

TABLE 3.—Results of Administration of Acetylsalicylic Acid in Fever Cases

Subject	Date	C.c. per Minute				Respiratory Quotient	Per Square Meter per Hour				Body Temperature		Pulse Rate	
		Carbon Dioxid Production		Oxygen Absorption			Calories Produced		Calories Eliminated					
		Control	Acetylsalicylic Acid	Control	Acetylsalicylic Acid		Control	Acetylsalicylic Acid	Control	Acetylsalicylic Acid	Change, C.	Initial, C.	Change per Min.	Initial per Min.
J. D.	1-24	....	161	....	202	0.80	....	38.7	....	54.4	—0.95	37.41	—14	70
	2-1	178	....	214	....	0.81	41.2	....	35.1	....	+0.41	37.20	+ 4	73
	2-26	....	170	....	193	0.88	....	37.8	....	52.6	—0.78	37.24	—12	80
G. G.	3-1	....	201	....	224	0.89	....	43.2	....	61.0	—1.07	38.41	— 8	108
	3-5	193	....	210	....	0.92	40.5	....	36.8	....	+0.21	38.27	— 6	108
	3-7	....	177	....	193	0.92	....	37.1	....	51.4	—0.80	37.20	— 2	85
G. M.	1-15	....	151	....	169	0.89	....	41.3	....	45.2	—0.41	37.69	—54	128
	1-16	153	....	181	....	0.85	43.4	....	41.0	....	+0.24	37.60	—11	100
T. W.	3-12	159	....	191	....	0.83	35.7	....	38.0	....	—0.14	37.75	0	88
	3-14	....	167	....	184	0.91	....	34.8	....	48.2	—0.83	37.75	— 4	84
Average	....	....	....	....	....	....	40.2	38.82	37.73	52.13				
Change	....	....	....	....	....	....	....	—3.9%	....	+38.2%				

it has been shown that heat elimination is not stimulated, by the antipyretic drug here tested, in normal persons, the hypothesis cannot stand in the form just stated. It was, nevertheless, considered of interest to determine whether or not the administration of dextrose with acetylsalicylic acid would tend to counteract the antipyretic action.

The result of giving 30 gm. dextrose with 1 gm. acetylsalicylic acid to a fever patient has been published elsewhere.[9] An unexpectedly profound fall in temperature (2 C. in two and one-half hours) took place. This exceeds by nearly 100 per cent. all effects noted from acetylsalicylic acid alone (Table 3), and soon led to the discovery that dextrose alone may exhibit antipyretic properties. Readily combustible material therefore is not necessarily a protection against the action of antipyretic drugs.

The dextrose work has led to a consideration of antipyretic action from the standpoint of the carbohydrate metabolism. Bearing on the question in hand is the effect which acetylsalicylic acid appears to exert, in fever cases but not in normal individuals, on the respiratory quotient. If it is true, as appears from the results described in this paper, that the drug causes an increased combustion of carbohydrates in fever patients and not in health, this fact may be of much significance in connection with the different response of the heat regulating mechanism in the two cases. It is necessary to develop this subject by further work.

CONCLUSIONS

1. Acetylsalicylic acid, in 1 gm. doses, which have no such action in normal persons, exhibits a marked antipyretic effect in febrile, temporarily afebrile and convalescent subjects.

2. In one and one-half hours the temperature change averaged —0.81 C. in six experiments on four individuals, as against an average rise of 0.18 C. on four control days.

3. In the control experiments the heat elimination averaged 37.7 calories per square meter per hour. Under acetylsalicylic acid it became 52.1 calories, an increase of 38.2 per cent. The antipyretic effect is due essentially to this change, which is associated with marked perspiration and subjective warmth.

4. The fall in temperature was accompanied by a heat production of 38.8 calories per square meter per hour, a decrease of 3.5 per cent. below the 40.2 calories of the control days. This change is probably merely the result of the cooling of the body.

5. The drug caused an averaged decrease in the pulse rate of ten beats per minute. Temporary cardiac disturbances were noted in two cases.

---

9. Barbour, H. G.: Proc. Soc. Exper. Biol. & Med. **16**:136, 1919.

6. The return to the initial temperature level is brought about essentially by a reduction of the heat elimination to about one half of the normal figure and is unaccompanied by shivering or marked increase in carbon dioxid output.

7. Sensitivity of febrile, temporarily afebrile and convalescent subjects to antipyretics is not yet explained. These drugs do not "stimulate" a "depressed" heat regulating mechanism, nor is sensitivity due to a lack of readily combustible material (dextrose); but the respiratory quotient of antipyretic sensitive individuals appears to be increased by doses of acetylsalicylic acid which do not affect the quotient of normal persons. Further studies of the carbohydrate metabolism may elucidate the question of sensitivity.

The present series of investigations has been made possible by the friendly assistance of Dr. Francis G. Benedict. He has given most generously of his time and advice, besides placing much material at my disposal. Dr. Carpenter and Miss Johnson of the Carnegie Nutrition Laboratory have also contributed many valuable suggestions. The best cooperation possible has been given by Dr. Cox, superintendent, and the members of the medical, surgical and dietetic staffs of the New Haven Hospital and especially by Dr. George Blumer.

Miss S. B. Plant, laboratory assistant, has given painstaking care to the many routine duties connected with the manipulation and upkeep of the apparatus and has made all of the calculations.

To all of these the author takes pleasure in expressing sincere thanks.

MENTAL DISORDERS FOLLOWING INFLUENZA*

ALFRED GORDON, M.D.
PHILADELPHIA

Infection and intoxication are morbid processes which are undeniably the fundamental causes of abnormal mental functioning in a large group of cases. It has been sufficiently demonstrated that endogenous and exogenous toxic substances are apt to create products fit only for elimination, but not for cellular life; and that their contact with nerve elements exercises an obnoxious influence on the function of the latter.

The function of the brain may also be disturbed by bacterial poisons which engender microbic and cellular toxins. Although the precise action of the latter on the nerve cell is still somewhat obscure, nevertheless, its existence is a matter of daily observation. What is absolutely certain in this entire problem is the fact that the organism always endeavors to get rid of the exogenous, endogenous and bacterial poisons either through the kidneys, lungs, salivary and cutaneous glands by direct elimination, or by means of modification and complete destruction by the cells of various tissues and organs, including the endocrine glands. Not infrequently amelioration of mental disorders runs parallel with the proper functioning of these defense organs when their activity is rendered energetic and prompt.

In the present contribution reference will be made to one of those infectious processes which, after the acute phase had subsided, produced evidently very profound disturbances in the higher functions of the cerebrum, thus corroborating the theory of pathogenesis given in the foregoing paragraph. A further evidence is furnished, moreover, by the fact that close therapeutic attention to the various glands and organs was followed by satisfactory results.

The following study is based on a series of sixty-two cases all seen at the end of the febrile period during the phase of asthenia which ordinarily follows infectious diseases. The majority of the cases (forty-four) presented the well known confusional type of psychosis, more or less pronounced. The mental manifestations were particularly marked in individuals whose previous medical histories either suggested various episodic phenomena of a neuropathic character or contained accounts of actual psychotic disorders. This particular group differed greatly from the groups of cases without previous nervous or mental disorders. Each group deserves a separate description.

---

* Read before the Philadelphia Psychiatric Society, March 14, 1919.

A. Cases With a Previous History of Psychopathic Traits.—The physiognomy of the patient is expressionless. The look is vague and cannot be fixed on any one object. The patient is entirely oblivious of his surroundings. He does not answer when spoken to, and when urged he will repeat the last word or sentence of the question. Then the speech is very slow. Memory is vague. Some patients could not tell their age, and whether they had families or not. They were very docile and could be led without the least objection or resistance.

Several patients presented delirium with hallucinations. These occurred only occasionally, and there was some systematization in the delusional conceptions, but the systematization was imperfect. The delusions were either of a hypochondriacal, or persecutory character. The delirium occurred in sudden outbursts, and disappeared suddenly. It was particularly observed in individuals with a previous history of acute or chronic alcoholism, and was invariably associated with hallucinations. The latter were auditory and visual, and mostly of a terrifying nature. As in other delirious states, the hallucinations were fleeting and changeable in their composition. The delusional conceptions likewise did not possess a fixed character. All the ideas of the patients were in a state of chaos without a trace of associative processes, and consequently the memory was very poor, especially with regard to recent events.

A highly interesting picture was presented by one patient in whom the struggle between the manifestations of an expansive state and the inability to associate ideas was most manifest. At one time he was greatly exalted, spoke or rather would commence to speak of his great accomplishments, but incoherence and confusion promptly interrupted his train of thought; he rapidly broke down and became morose and quiet. This interruption occurred invariably when he attempted to recite his great deeds in the line of banking. It was evident that the confusion of ideas was the fundamental disturbance, and it was so profound that it interfered not only with the expression of thoughts, but with the expression of the emotions, this being evident also in the attitude and demeanor as well as the facial expression of the patient. It also gave color to the changes in the physical reactions. The digestive functions were most capricious; at times, they were most excellent, at others, very poor; constipation alternated with diarrhea. At times the muscular system presented hypotonia and sometimes hypertonia. In the first case there was a general relaxation so that station was difficult, the arms hung alongside the body; the face was without expression and saliva ran out of the mouth. In the second case there was hypertonia in the form of catatonic manifestations. Vasomotor

disturbances were present (erythemata), but they were of a variable character. The tendon reflexes were invariably increased.

B. Cases Without Morbid Previous Histories. — While the confusional element was present in these cases also, it was not so intense as in the previous group. The patient presented a physiognomy without reactions, but he frequently could be raised out of his confusional state when under the influence of some stimulating factor. However, this was transitory and the patient rapidly returned to his fundamental condition.

This group of cases differs also from the first group in that at no time during the entire course of the disease, hallucinations were present. It corresponds to Kraepelin's "asthenische Verwirrtheit" in contradistincton to the "halluzinatorische Verwirrtheit" of Meynert which covers the first group of cases. Besides the absence of hallucinations and the slight intensity of the confusion in the second group, the course of the affection was different in the two series of cases. In the first group the confusional state was protracted; in some patients who had before pretended similar outbreaks, the present attack was more pronounced than all previous ones. Both groups of cases presented various degrees of intensity, but it was especially in the first series that several varieties occurred. There was present in some of these cases a hallucinatory confusional state of a depressive character without systematization in the vague delusions or else with systematization. There were also cases of confusion with agitation, with and without delusions; finally cases occurred without hallucinations.

The second group of cases were all identical in their essential characteristics, the difference lay only in the degree of confusion and difficulty in associating ideas.

Unusual Features of Other Cases.—The remaining (eighteen) cases of the entire series of the present study were especially instructive by reason of some unusual features. In each of them the most conspicuous symptom was *amnesia* of a pronounced character. Every one of them had great difficulty in recalling names of important places and persons, or names of nearest relatives; some of them could not tell the number of their children, some did not know the days of the week, let alone the date, month and even year. With regard to the year, in some cases the error was as much as twenty years difference. Some patients could not recall even facts which had occurred almost immediately before being questioned, such as having taken food, as having read a newspaper, etc. They were all conscious of their amnesia, and made an effort to correct the defect and recall the forgotten facts, but in vain. At no time until the phase of improvement commenced, could they bring back to memory events in which they

participated even when attempts were made to aid them in their efforts by associating the forgotten facts with ideas which had a bearing on them.

In addition to the amnesia which was the most prominent symptom in this small group of cases, we should add that the entire mental attitude of the patients was that of individuals who are recovering from a protracted disease. There was a *mental asthenia,* so to speak. It was a tremendous effort for them to think, to respond to questions, to comprehend what was said to them. The mental strain which they were undergoing was visible in their facial expression, in their movements, and general behavior. It seems that the above mentioned inability of recalling facts was closely connected with and dependent on the asthenia. Just as it was difficult for them to associate ideas and reflect while being interrogated, so it was difficult for them spontaneously to bring back to memory facts and events. The amnesia, therefore, was merely a manifestation of the cerebral asthenia.

It was interesting to observe that when amelioration of condition commenced to make its appearance, a parallel and proportionate improvement was observed in all the manifestations, that is in the amnesia, etc. As memory is normally dependent on the facility of associating former impressions at any desired moment, loss of memory or deficient memory is in intimate relation with the loss of that capacity. As the cerebral asthenia of the patients was manifested in a difficulty in all mental operations, the amnesia was the natural result. The amnesia, therefore, could not be considered as having an independent existence, but only as one of the manifestations of a general cerebral condition caused by a post-infectious toxic state.

To recapitulate: Of the mental states observed in this series of cases one may mention three varities: (A) a profound confusional psychosis with delusions and hallucinations; (B) a mild confusional state without hallucinations but with illusional conceptions, and (C) cerebral asthenia with conspicuous amnesic phenomena.

CLINICAL COURSE

The course of these three conditions is not without some interest. In the first group a small number recovered (three), and the recovery was rapid; but the others are still under observation. They present alternating periods of improvement and of return to the original condition, and apparently show no tendency to recovery. The non-hallucinatory type presents a more promising outlook than the hallucinatory form; the amelioration of the symptoms being more evident and their intensity less pronounced. The above mentioned three recoveries occurred in cases which did not present hallucinations.

In the second variety of confusional psychosis in the series, while the symptoms were less intense than in the first, the cases nevertheless presented a longer duration than the three cases of the first group which made a recovery. The amelioration in the mental condition ran parallel with the improvement in the general physical state of health. The course of the psychosis was exceedingly slow, and for some time after the confusional element had disappeared there remained a certain degree of weakened attention and the exercise of the intellectual functions remained somewhat difficult. Eventually, however, the latter disappeared and the recovery was complete.

The last group of cases in the series which presented amnesia was composed of the asthenic cases. Their course resembled largely that of the previous group. The improvement in the memory coincided with the amelioration in other mental functions, and both ran parallel with the condition of the general asthenia. Simultaneous improvement and eventual recovery took place in all directions. The recovery was somewhat more rapid than in the second group of cases.

CONCLUSIONS

The observation made in the last two groups, concerning the parallel course of the various manifestations in the mental sphere and of those in the physical condition, also the parallel improvement, suggest at least a relationship between both groups of phenomena. On the other hand, the circumstances under which confusion ordinarily occurs, namely, in infections and intoxications, especially of internal origin, warrant the assumption that the nutrition of the cerebral neurons is altered by the altered composition of the body fluids which necessarily occurs in toxic states. That microscopic changes may take place in the cortical cells during a confusional state caused by toxic substances irrespective of their origin, had been demonstrated by Ballet. In the confusional psychosis which accompanies multiple neuritis and which is known under the name of Korsakoff's psychosis, he found cell changes in the cortex, namely, tumefaction and deformities, chromatolysis and disappearance of the nuclei (*Sem. méd.*, p. 284, 1898). This organic basis is logically applicable to the incurable cases. In the milder and curable ones we may suppose that the toxins produce a transitory functional disorder in the cells which promptly disappears, so that the cells rapidly recover their normal function. But it is to be assumed that both the functional and organic disorders of the cells are the result of intoxication. The latter may be observed in any of the infectious processes, of which influenza is one.

1812 Spruce Street.

THE ELECTROCARDIOGRAM AND VENTRICULAR PREPONDERANCE *

EDWARD PERKINS CARTER, M.D.
AND
CARL H. GREENE, PH.D.
BALTIMORE

Following Einthoven's[1] first description of the characteristic directional changes in the R wave, in lead III, associated with aortic or mitral disease, the applicability of the electrocardiograph to the study of alterations in the size of the heart has been severely questioned. Clinical observers have held widely differing views in regard to the value of the so-called electrocardiographic signs of hypertrophy. That there are many cases in which the electrocardiograms do not agree with the clinical evidence has been recognized. Bridgeman[2] has called attention to the fact that in general the English and American observers have accepted the electrocardiographic evidences of hypertrophy, while the German authors placed but little reliance on these findings.

Classification of this mass of conflicting evidence began with the calculation of the direction of the electrical axis of the heart by Einthoven, Fahr, and de Waart.[3] These authors find that in normal individuals the electrical axis of the heart roughly corresponds to the anatomic axis at an angle between 40 and 90 degrees from the horizontal. Somewhat comparable changes occur in the two axes on mechanical displacement of the heart by change in posture, the greatest difference in the electrical axis being between the right-sided and left-sided prone positions. Lesser differences are noted between the upright and horizontal. The greatest mechanical changes in the electrical axis of the heart are those due to the respiratory movements for the angle α increases with inspiration and decreases with expiration, the degree of change varying between 5 and 30 degrees. Waller[4] reports similar variations in the axis, though he considers the normal to show a greater range of variability, i. e., from 10 to 100 degrees with 60 degrees considered as the typical angle.

---

* From the Cardiographic Department of the Johns Hopkins Hospital and University.

1. Einthoven, W.: Arch. internat. de physiol. **4**:132, 1906.
2. Bridgeman, E. W.: Arch. Int. Med. **15**:487 (April) 1915.
3. Einthoven, W., Fahr, G., and de Waart, A.: Arch. f. d. ges. Physiol. **150**:275 1913.
4. Waller, A. D.: Proc. Roy. Soc. Lond. **138**: B, 49 1914.

In his interpretation of the meaning of these differences in the electrical axis of the heart, Waller[5] contents himself with a classification into those hearts with a vertical and those with a horizontal axis. These two types he speaks of as the vertical or youthful heart and the horizontal or drop heart and considers them as more or less identical with the same types observed roentgenographically. Einthoven, Fahr and de Waart, however, believe that the study of the electrical axis of the heart is of definite clinical value, and postulate that when the degree of change from the normal is too great to be explained by simple anatomic displacement, the explanation must be sought for in a hypertrophy of the corresponding ventricle.

Lewis,[6] in attempting to apply the Einthoven criteria of hypertrophy, clinically, was struck by the discrepancies between the electrocardiographic and the clinical evidence; a condition that led him into a careful study of cardiac hypertrophy. By an exact record of ventricular weights he was able to point out not only the inaccuracies of the ordinary clinical signs of ventricular hypertrophy but also the impossibility of judging ventricular preponderance at the postmortem table with any reasonable degree of accuracy. More important still, in those cases in which complete data were available, he was able to point out the close relationship between the electrocardiographic findings and the ventricular weights. Concluding, Lewis[7] emphasizes the fact that the electrocardiogram gives evidence not of hypertrophy of the heart as such, but rather of preponderance of one ventricle or the other.

"The point which it is desired to emphasize is that the term preponderance is employed irrespective of the weight of the whole heart. . . . It is an altered (weight) ratio (between the two ventricles) and that alone which conditions the form of the electrocardiograms to be described."

In this study of ventricular hypertrophy, Lewis made use of an arbitrary formula in determining the degree of electrical preponderance. This formula has recently been amplified by White and Bock[8] in an effort to secure a quantitative measure of the degree of preponderance. Their index is determined according to the formula:

$$(U_1 + D_3) - (D_1 + U_3) = \text{Index}$$

U equals the amplitude of the chief upward excursion of the QRS group of the corresponding lead.

D equals the amplitude of the chief downward excursion of the QRS group of the corresponding lead. White considers an index of

5. Waller, A. D.: Proc. Roy. Soc. Lond. **136**: B, 507, 1913.
6. Lewis, T.: Heart **5**:367, 1914.
7. Lewis, T.: Clinical Electrocardiography, London, 1919, p. 30.
8. White, P. D., and Bock, A. V.: Am. J. M. Sc. **156**:17 (July) 1918.

+ 20 or over as indicative of a left ventricular preponderance, while an index from — 15 to — 18 or more is characteristic of a right ventricular preponderance.

In a recent article from this laboratory[9] we have drawn attention to a graphic method for the rapid and accurate determination of the inclination of the electrical axis of the heart. We find this to be the most accurate method for the quantitative determination of ventricular preponderance. In brief, measurements are made of the RS wave in each of the different leads. Then, on the general assumption that the deflection represents the resultant of opposing or balanced electrical currents from the two sides of the heart, the net movement of the string is determined by subtraction of the downward deflection in each lead from the upward. These measurements and the basic assumption are the same as those that underly the determination of the index of Lewis or White. However, instead of the calculation of an index by the total movement of the galvanometer string, the net deflections in leads I, II and III are used to reconstruct the Einthoven triangle and to determine graphically the direction of the electrical axis in the heart. This reconstruction gives not only α, but the manifest value of the potential difference (E) as well. It is in ignoring this latter point that the White index becomes theoretically unsound, for the potential change observed in any lead of the electrocardiogram depends on both the total potential difference in the heart (E) and the direction of the electrical axis α. Theoretically, for any given value of E the White index would be greatest when α equals — 30 or + 150 degrees, while when α equals + 60 degrees the index would be zero regardless of the size of E. According to the normal limits stated by White, a left ventricular preponderance is indicated when $E = 11.5$ if $\alpha = -30$ degrees, but if $E = 23$, then an equal degree of preponderance is indicated though $\alpha = +30$ degrees. Similarly, when $\alpha = +150$ degrees a right ventricular preponderance is not indicated unless E is at least 8.6 while at + 90 degrees a value for E of 17.3 or more would nevertheless show ventricular change. Our greatest difficulty in the use of the White index has not been that of false indications with great potential differences in the heart but rather with the prevalence of such small values of E that positive change in the index was impossible regardless of α. In such cases the ventricular preponderance can only be determined by a calculation of the direction of the electrical axis.

The present series of cases of ventricular preponderance were secured in the course of about 200 routine examinations made in the

9. Carter, E. P., Richter, C. P., and Greene, C. H.: Bull. Johns Hopkins Hosp., **30**:162 (June) 1919.

cardiographic department of the Johns Hopkins Hospital. For the most accurate determination of α the records in the different leads should be synchronized to avoid phasic variations between the several derivations. Measurements should also be taken at identical periods in the respiratory cycle. Such refinements of technic were not possible in the present instance, nor are they desirable, except in physiologic experimentation of the greatest exactitude.

As a routine procedure, the measurements of several successive peaks were averaged in order to secure a mean value of α independent of possible respiratory variation. Usually, such measurements obeyed the Einthoven law ($E_1 + E_3 = E_2$) or else the error due to phasic differences between the three leads was so slight as to permit of the selection of a mean value of α. In those few cases in which marked discrepancy existed, α was determined from the measurements in leads I and III, lead II being ignored. When determined in this manner, the values of α are accurate to within 5 degrees in all cases except those showing the most pronounced phasic variation. A greater degree of accuracy is unnecessary in ordinary clinical routine though it is desirable to secure values closer than the 60 degrees approximations secured by simple inspection as pointed out by Pardee.[10]

We have arbitrarily chosen 0 and $+90$ degrees as representing the extremes of the normal values of α. While these limits were set largely as a matter of convenience and are slightly greater than those of Einthoven, Fahr, and de Waart, they nevertheless lie within the normal values of Waller. In view of the present uncertainty of the exact dividing line between normal and pathologic hypertrophy, especially of the left ventricle, these values may be considered to be sufficiently accurate to serve for the present.

Table 1 shows the electrocardiographic findings in this series as compared with the physical findings and the clinical impression. Examination shows that there is no relationship between the degree of ventricular preponderance and the limits of the relative cardiac dulness. In all of these cases the great variability and consequent nonreliability of the White index is to be pointed out.

As a means of accurate measurement and diagnosis of cardiac size and position, the percussion of the relative cardiac dulness has more recently given way to the orthodiagram and the teleroentgenogram. That these roentgenographic methods fail to give an insight into the question of the preponderance of the ventricles is shown in Table 2. Bardeen,[11] in a recent exhaustive study of the teleroentgenogram, points out that owing to the differing positions of the heart within

10. Pardee, H. E. B.: J. A. M. A. **62**:1311 (April 25) 1914.
11. Bardeen, C. R.: Am. J. Anat. **23**:423 (March) 1918.

the chest, measurement of the cardiac borders fails to give a true impression of local changes in the heart. He does show, however, that the area of the cardiac shadow is a true index to hypertrophy of the heart as a whole. From the area of the shadow, Bardeen is able to calculate very accurately the cardiac volume and, though less accurately, the weight. It has been recognized that while the teleroentgenogram may give the best index to hypertrophy, it is nearly always

TABLE 1. — COMPARISON OF ELECTROCARDIOGRAPHIC AND PHYSICAL FINDINGS

Case No.	Electrocardiographic Preponderance		Relative Cardiac Dulness		Clinical Impression
	a°	White Index	Right, Cm.	Left, Cm.	
2240	— 5	+15.0	4.0	14.0	Aortic stenosis and insufficiency; hypertension; ascites
2242	— 5	+21.0	4.5	15.0	Myocardial insufficiency; hypertension; chronic nephritis
2245	— 5	+17.5	4.0	12.5	Aortic insufficiency; syphilis; right hydrothorax
2272	— 5	+ 9.5	4.0	15.5	Hypertension with dilatation; aneurysm of arch
2269	— 10	+10.0	5.5	17.0	Aortic insufficiency; myocardial insufficiency; endocarditis; syphilis
2245	— 10	+ 7.0	3.0	11.0	Aortic roughening; chronic myocarditis; arteriosclerosis; syphilis
2247	— 15	+11.5	4.0	11.5	Myocardial insufficiency; chronic nephritis; hypertension
2230	— 20	+17.0	5.0	17.0	Myocardial hypertrophy and insufficiency; hypertension
2260	— 25	+12.0	5.0	17.0	Myocardial insufficiency; hypertension; chronic nephritis
2222	— 30	+12.0	5.0	15.5	Aortic insufficiency; myocardial insufficiency
2243	— 30	+ 8.0	5.5	13.0	Myocardial insufficiency; hypertension; arteriosclerosis
2277	— 35	+20.0	5.0	17.0	Myocardial insufficiency with dilatation; colloid goiter
2274	— 45	+ 8.0	3.0	15.0	Myocardial insufficiency with dilatation; hypertension
2252	— 60	+ 8.0	4.0	....	Myocardial insufficiency; hypertension; syphilis
2255	—110	+ 6.5	5.5	15.0	Myocardial insufficiency; hypertension; chronic nephritis
2257	—140	— 9.5	4.5	15.0	Myocardial insufficiency; essential hypertension; arteriosclerosis
2275	+ 95	— 3.0	2.5	18.0	Myocardial insufficiency; atrial fibrillation
2271	+100	—16.5	3.5	7.5	Mitral stenosis and insufficiency; chronic endocarditis
2310	+105	—15.5	0.0	10.0	Right pneumothorax
2264	+105	— 5.5	4.0	12.0	Tuberculous peritonitis
2256	+115	— 5.0	5.0	15.0	Mitral stenosis and insufficiency; myocardial insufficiency
2275	+120	— 3.0	4.0	12.0	Myocardial insufficiency; hypertension
2291	+140	—11.0	5.0	12.0	Mitral stenosis and insufficiency; pericarditis; endocarditis
2231	+150	— 2.0	2.0	7.0	Tuberculous peritonitis; right pleurisy

silent in regard to the part played by the different chambers of the heart in this hypertrophy. Morison and White[12] have tried to throw light on this point by the use of oblique illumination and an estimation of the depth of the cardiac shadow. Any increase they believe to be an early and valuable sign of hypertrophy, especially of the left ventricle. Such results while valuable, however, lack the definiteness of the electrocardiographic indications.

12. Morison, J. M. W., and White, L.: Arch. Radiol. & Electroth. **23**:282 (Feb.) 1919.

The crucial experiment in such a study as the present is the direct comparison of the electrical axis with the ventricular weights, directly determined. Such a comparison is made possible by the experiments of Lewis[6] and of Cotton,[13] each of whom has published a short series of parallel determinations of the electrocardiogram and the ventricular weights. These results are shown in Table 3. In general, a very good agreement is evident between the degree of electrical preponderance indicated by the weight ratio. Three marked exceptions to this rule occur: Lewis, No. 109, and Cotton, Nos. 101 and 225. Of these three, the Lewis No. 109 presents a slightly peculiar electrocardiogram in that the measurements given indicate a practically diphasic RS curve in each of the three leads. The exact bearing of this rather peculiar type of curve cannot be explained in the light of

TABLE 2.—COMPARISON OF ELECTROCARDIOGRAPHIC AND ROENTGENOGRAPHIC FINDINGS

Case No.	Electrocardiographic Preponderance		Teleroentgenographic Measurements		Case No.	Electrocardiographic Preponderance		Teleroentgenographic Measurements	
	α°	White Index	Right, Cm.	Left, Cm.		α°	White Index	Right, Cm.	Left, Cm.
2253	— 5	+10.5	4.5	8.7	2235	— 30	+ 2.0	4.1	7.7
2340	— 5	+ 7.0	3.4	8.4	2233	— 35	+12.5	4.5	9.9
2347	— 5	+ 4.0	6.1	9.8	2236	— 35	+11.0	4.9	9.0
2208	—15	+ 6.0	4.1	8.3	2250	— 40	+28.0	4.5	10.5
2234	—15	+15.0	3.5	10.3	2237	— 40	+ 8.0	5.4	12.3
2247	—15	+11.5	4.0	9.0	7902	— 60	+15.0	5.0	10.4
2206	—15	+11.0	5.0	10.9	2255	—110	+ 6.5	5.0	11.5
2308	—15	+10.0	3.5	8.8	2313	+100	—10.0	3.2	7.3
2230	—20	+17.0	3.0	7.5	2264	+105	— 5.5	3.0	9.0
2251	—20	+12.0	2.5	10.0	2328	+115	— 9.0	2.3	9.6
2318	—20	+14.5	4.8	8.4	2272	+135	— 6.0	5.5	13.0
2252	—25	+26.0	5.4	9.7	2266	+150	—13.5	3.5	9.5
2336	—25	+12.0	5.6	13.3					

our present knowledge of the electrocardiogram. In the two cases reported by Cotton the graphic records were taken some time before death, and he suggests that change may have occurred in the interim. Stewart[14] has demonstrated in dogs, that changes in the ventricular weights may be found within a week after experimental lesions of the valves. In view of these experiments, the validity of Cotton's explanation may be assumed. If these three questionable cases are eliminated from the series, then the agreement becomes very close indeed. It was this agreement that led Lewis to emphasize the electrocardiograph as a means of determining the relative mass of the two ventricles.

Recently, in a preliminary report, Fahr[15] stated that the direction of the RS wave in the electrocardiogram is dependent on the

13. Cotton, T. F.: Heart **6**:217, 1917.
14. Stewart, H. A.: J. Exper. M. **13**:187, 1911.
15. Fahr, G. E.: J. Mich. M. S. **17**:10 (Jan.) 1918.

relative length of the conduction system and the consequent relative time of propagation of the excitation wave in the two sides of the heart. In continuation, he states the possibility in cases of dilatation, of calculating the directional relationships of the RS wave from measurements of the two branches of the bundle of His. According to Fahr, therefore, the electrocardiographic signs of preponderance are directly related to changes in ventricular volume rather than mass, and so indicate relative dilatation instead of relative ventricular hypertrophy as claimed by Lewis, and, as it seems to us, substantiated by the published cases of Lewis and Cotton (Table 3).

TABLE 3.—Comparison of Electrocardiographic and Necropsy Findings

Author	Case No.	Electrocardiographic Preponderance		Ventricular Weights, L — Ratio R	Pathologic Diagnosis
		α°	White Index		
Lewis	109	— 90	+ 1.5	1.38	Aortic disease with mitral stenosis
Cotton	265	— 70	+17.5	2.55	Renal disease
Lewis	110	— 60	+19.0	2.60	Angina pectoris
Cotton	147	— 30	+29.5	2.63	Renal disease
Cotton	225	— 25	+ 9.0	1.55	Renal disease
Lewis	2	— 10	+21.5	2.04	Aortic disease
Lewis	107	+ 5	+12.5	1.87	Aortic disease
Lewis	59	+ 25	+ 5.5	1.82	Mitral stenosis and aortic disease
Lewis	58	+ 30	+ 8.0	1.94	Renal disease
Cotton	236	+ 80	— 3.5	1.30	Mitral stenosis
Cotton	101	+ 85	—10.0	1.97	Renal disease
Lewis	60	+120	— 7.0	1.09	Mitral stenosis and aortic disease
Lewis	63	+135	—15.5	0.82	Mitral stenosis and atrial fibrillation
Lewis	...	+140	—77.0	0.41	Congenital pulmonary stenosis
Cotton	189	+170	— 6.0	0.82	Mitral stenosis

It is hoped that further evidence bearing on this point may be presented later, though in view of the close relationship existing between dilatation and hypertrophy in any long standing process, this exact differentiation is, after all, rather an academic question.

SUMMARY

It may again be emphasized that the electrocardiogram is the only satisfactory clinical method capable of estimating the relative preponderance of the two ventricles. Combined with the teleroentgenogram as a guide to gross hypertrophy of the heart, it should furnish the clinician with an increased insight into the question of the mechanics of cardiac response in cases of hypertrophy.

In view of the ease of determination of the inclination of the electrical axis of the heart it is hoped that further work may be stimulated with a view to deciding its value as a quantitative guide to cardiac change.

THE BASAL METABOLISM IN EXOPHTHALMIC GOITER *

J. H. MEANS, M.D., AND J. C. AUB, M.D.

BOSTON

CONTENTS

1. INTRODUCTION.
2. HISTORICAL.
3. METHODS.
4. CLINICAL AND METABOLISM DATA.
   A. Controls:
      (a) Normal (Table 1).
      (b) Miscellaneous Diseases (Table 1).
      (c) Nontoxic Goiters (Table 2).
      (d) Borderline Cases and Differential Diagnosis (Table 3).
   B. Exophthalmic Goiter:
      (a) Roentgen-Ray Series (Table 4).
      (b) Surgical Series (Table 5).
      (c) Miscellaneous Series (Table 6).
5. INTERPRETATION OF DATA.
   A. Effect of Rest.
   B. Effect of Roentgen Ray.
   C. Effect of Surgery.
   D. Roentgen-Ray and Surgery Compared.
   E. Relation of Metabolism to Other Factors.
   F. Metabolism as a Guide to Treatment.
6. CONCLUSIONS.

INTRODUCTION

Four and one half years ago a study of the basal metabolism in exophthalmic goiter was started at the Massachusetts General Hospital. Preliminary reports on this work appeared in June, 1916,[1] and in July, 1917.[2] It was impossible for us at the latter date, because of the imminence of mobilization, to present more than the barest outline of our work, together with the conclusions drawn to that time.

The original program of the research was to follow the metabolism and clinical condition of a series of cases of exophthalmic goiter over a period of several years, during which time the patients would be undergoing therapy of one sort or another. This was carried out to

* Received for publication Oct. 1, 1919.

*From the Medical Service of the Massachusetts General Hospital and the Medical Department of the Harvard Medical School, aided in part by a grant from the Proctor Fund, Harvard University.

1. Means, J. H.: Studies of the Basal Metabolism in Disease, Boston M. & S. J. **174**:864 (June 15) 1916.

2. Means, J. H., and Aub, J. C.: Study of Exophthalmic Goiter from Point of View of the Basal Metabolism, J. A. M. A. **69**:33 (July 7) 1917.

the end of April, 1917. Then, during the two years of the war, the patients, for the most part, disappeared from observation, although nine were seen once during that time.[3] Since our discharge from the service in March, 1919, we have made every effort to locate these patients and to get them to the hospital for further observations. Of the total cases of toxic goiter, fifty-five in number, which comprised the original series, nine patients are known to be dead, twenty-four have recently had basal metabolism determinations, ten more have been seen or heard from, and twelve are lost.

The purpose of the present paper, then, is twofold: in the first place, we wish to present in full the data that we outlined in previous papers, and secondly, to present and discuss the data recently secured. Our discussion is based on 345 metabolism observations on 130 patients.

HISTORICAL

For the purposes of this paper, an exhaustive résumé of the literature is not necessary.

On the subject of the gas exchange in thyroid disease, the German literature, beginning with Magnus-Levy,[4] is voluminous; the American literature is scanty. DuBois[5] unquestionably is the pioneer in this country, and in his paper a review of the German literature will be found. Following DuBois we,[1, 2] also Boothby,[6] and very recently McCaskey,[7] have emphasized the importance of basal metabolism determinations as an index of toxicity in hyperthyroidism.

We believe that our own work is the first in this country in which the metabolism of patients with exophthalmic goiter has been followed before treatment, and for periods of two or more years after treatment.

It would obviously be out of place to discuss the vast literature of the surgery or of the roentgen-ray treatment of the thyroid. An account of the early work in roentgen-ray treatment of exophthalmic goiter at the Massachusetts General Hospital has been published by Seymour.[8]

---

3. These observations were kindly made for us by Dr. Harry Linenthal, assisted by Miss Catherine Thacher.

4. Magnus-Levy, A.: Gaswechsel bei Thyroidea, Berl. klin. Wchnschr. **32**: 650, 1895.

5. DuBois, E. F.: Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**: 915 (June) 1916.

6. Boothby, W. M.: Clinical Value of Metabolic Studies in Thyroid Cases, Boston M. & S. J. **175**:564 (Oct. 19) 1916.

7. McCaskey, G. W.: The Basal Metabolism and Hyperglycemic Tests of Hyperthyroidism with Special Reference to Mild and Latent Cases, J. A. M. A. **73**:243 (July 26) 1919.

8. Seymour, M.: Treatment of Graves' Disease by the Roentgen Rays, Boston M. & S. J. **175**:568 (Oct. 19) 1916.

The whole subject of the relation of the thymus gland to exophthalmic goiter has been set forth by Halsted in a Harvey Lecture.[9] Halsted predicts that for roentgen-ray and radium treatment there is a great future, particularly because of the important rôle of the thymus in the causation of exophthalmic goiter, and the profound effect of irradiation on that gland. Other writers, Boggs[10] for example, have reported good results with the roentgen ray, especially when the thymus gland is exposed as well as the thyroid.

METHODS

The methods used will merely be mentioned, having been described and discussed in previous papers.[1, 11, 12]

The gas exchange of normal individuals resting, and in the post-absorptive condition, has, with certain recognized variations due to age and sex, been found to be very constant if expressed in terms of their body surface.[13, 14] The gas exchange of patients with hyperthyroidism, on the other hand, is elevated above the normal. We have used the degree of elevation as a measurement of the degree of thyroid intoxication.

The basal gas exchange was determined with the Benedict universal respiration apparatus, and the heat production was calculated therefrom. Through April, 1917, we used the calorific value of oxygen for the respiratory quotient obtained; in those calculations after that time we determined oxygen only and assumed an R. Q. of 0.82.

The body surface was determined from DuBois' height weight chart,[15] except in a few instances early in the work, where the linear formula[16] was used.

---

9. Halsted, W. S.: Significance of the Thymus Gland in Graves' Disease, Harvey Lectures, 1913-14, p. 224.

10. Boggs, R. H.: Treatment of Goiter by Roentgen Rays, Interstate M. J. **24**:362 (April) 1917.

11. Palmer, W. W.; Means, J. H., and Gamble, J. L.: Basal Metabolism and Creatinin Elimination, J. Biol. Chem. **19**:239, 1914.

12. Means, J. H.: Studies of Basal Metabolism in Obesity and Pituitary Disease, J. M. Research **32**:121, 1915.

13. Means, J. H.: Basal Metabolism and Body Surface, J. Biol. Chem. **21**: 263, 1915.

14. Gephart, F. C., and DuBois, E. F.: Basal Metabolism of Normal Adults with Special Reference to their Surface Area, Arch. Int. Med. **17**:902 (June) 1916.

15. DuBois, D., and DuBois, E. F.: Formula to Estimate Approximate Surface Area, Arch. Int. Med. **17**:863 (June) 1916.

16. DuBois, D., and DuBois, E. F.: The Measurement of the Surface Area of Man, Arch. Int. Med. **15**:868 (June) 1915.

The roentgen-ray treatments were given at the Massachusetts General Hospital by Drs. G. W. Holmes and A. S. Merrill and we understand that they will publish an account of the work from the point of view of the roentgenologist with full particulars as to methods. The thyroid and thymus glands were both exposed at each treatment to nearly the maximum dose the skin would stand. The treatments were given from three to four weeks apart, as a rule, though sometimes a longer gap would occur.

The surgical operations, unless otherwise stated in the tables, were performed by Dr. C. A. Porter at the Massachusetts General Hospital. Almost without exception, the operations consisted in either ligation of the superior vessels or in partial thyroidectomy. The word lobectomy as we have used it in the tables indicates a partial thyroidectomy.

CLINICAL AND METABOLISM DATA

Our work is set forth in a series of tables. These, though voluminous, have been purged of all but essential data.

In the matter of figures, we have endeavored to give as few as possible. In case two figures are derivable, one from another, but one has been shown. Thus, the patient's age, sex, height and weight are given, but his surface area is not. If anyone wishes the area he has but to turn to DuBois' chart.[15] The oxygen absorption not being interesting per se is omitted, but the calories per square meter per hour, which are derived from it, are shown. The carbon dioxid and respiratory quotient are not given, because they do not enter directly into the present problem. They may be published later. In all periods used the quotients were within normal limits.

To determine the variation from the normal metabolism we have used the standards, which have been adopted by the Russell Sage Institute,[17] which take into account the variations due to age and sex. Our figure for the variation of the metabolism from the normal is the percentile variation above or below (expressed by + or —) the appropriate one of these standards. The really essential figures for purposes of discussion are the percentile variation from the normal metabolism, the pulse rate and the body weight.

We will now proceed with a running account of the material contained in the several tables, adding such clinical notes as the occasion seems to demand and later we shall analyze the data contained therein.[18]

---

17. Aub, J. C., and DuBois, E. F.: Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (June) 1917.

18. In the text and in the tables all patients are referred to by our laboratory numbers. They were referred to by the same numbers in our earlier paper, and will be in future papers, hence can readily be identified.

Controls.—Normal controls have appeared in earlier papers. A certain number of pathologic controls have likewise been obtained. In Table 1 are collected the data on twenty-two such cases, together with that of three normals (Nos. 7, 43 and 44). We do not pretend, of course, that alterations in the metabolism are confined to thyroid disease. It is a well known fact that they occur in other ductless gland disturbances and in blood diseases, also in acidosis and fever. Table 1 is interesting, however, in that it shows a variety of abnormalities in which there is little, if any, variation from the normal. Two cases of neurasthenia (Nos. 1 and 119) and one of a psychoneurosis (No. 109) all vary less than 10 per cent. from the normal. The same is true in such conditions as myasthenia gravis (No. 4), Raynaud's disease (No. 8), elephantiasis (No. 11), acroparesthesia (No. 14), Addison's disease (No. 20), and metrorrhagia (No. 69). A case of pernicious anemia (No. 17) and one of secondary anemia (No. 108) were also within normal limits. A rise is often found in pernicious anemia,[19, 20] but in our case, just mentioned, it will be noted that there was not a very severe degree of anemia at the time the observation was made. Two cases of tachycardia of unknown origin (Nos. 19 and 50) varied only 5 and 11 per cent., respectively, above the standard. A case of irritable heart (No. 158) was quite within normal limits. A case of paroxysmal tachycardia (No. 67) showed a definite elevation, and it is interesting to note that the elevation is greater during an interval than during a paroxysm. Two cases of obesity (Nos. 47 and 58) were quite within normal limits. This is additional evidence in favor of the view expressed by one of us (J. H. M.) in an earlier paper[21] that there is no fundamental change in the basal metabolism in obesity. An inactive acromegalic (No. 122) was also normal. Of two diabetics, one (No. 55) showed a normal figure, the other (No. 56) a slight reduction. This last patient, however, had been starving for over four days, so this reduction was quite what we should expect. A case of psoriasis in an elderly woman (No. 94) showed a rise of 12 per cent., and a case of pelvic inflammation and phlebitis (No. 124) showed a rise of 8 per cent., which is within the range of normal variation.

---

19. Meyer, A. L., and DuBois, E. F.: Basal Metabolism in Pernicious Anemia, Arch. Int. Med. **17**:965 (June) 1916.

20. Tompkins, E. H.; Brittingham, H. H., and Drinker, C. K.: Basal Metabolism in Anemia, Arch. Int. Med. **23**:441 (April) 1919.

21. Means, J. H.: Basal Metabolism in Obesity, Arch. Int. Med. **17**:704 (May) 1916.

TABLE 1.—METABOLISM DATA. CONTROL CASES

No.	Date	Sex	Age	Weight, Kg.	Height, Cm.	Pulse	Calories per Square Meter per Hour	Percentile Variation from Standard	Remarks
1	6/10/14	♂	22	63.2	185.5	88	41.2	+ 4	Neurasthenia
	6/11/14	♂	22	63.2	185.5	79	39.8	0	
4	10/19/14	♀	22	36.3	.....	75	30.5	— 1	Myasthenia gravis
7	12/ 3/14	♀	60	69.3	.....	67	31.5	— 7	Normal
8	2/18/15	♀	40	50.7	165.0	74	35.5	— 1	Raynaud's disease
11	5/24/15	♀	18	55.0	157.5	84	36.4	— 4	Elephantiasis
14	4/ 6/15	♀	60	65.0	150.0	67	36.1	+ 2	Acroparesthesia
17	4/20/15	♂	41	51.7	162.0	70	37.1	— 4	Pernicious anemia. Hg 70%, R. C. 2.9 mil.
19	4/26/15	♂	55	70.0	.....	98	39.3	+ 5	Tachycardia of unknown origin
20	5/ 6/15	♂	31	62.0	.....	62	42.0	+ 6	Addison's disease
43	11/18/15	♂	19	71.3	175.0	60	44.0	+ 7	Normal
44	11/19/15	♀	22	62.1	156.0	78	42.6	+15	Normal
47	12/18/15	♀	25	77.5	160.0	65	38.3	+ 3	Obesity
50	1/12/16	♂	32	54.0	172.5	105	45.8	+11	Tachycardia of unknown origin
55	2/18/16	♀	47	55.0	161.8	80	35.3	— 2	Diabetes not sugar-free, alveolar CO_2 33.3 mm.
56	2/19/16	♀	56	49.5	162.0	59	31.2	—14	Diabetes sugar-free, 5th day of fast; alveolar CO_2 29.4 mm.
58	4/ 1/16	♀	38	109.0	159.0	80	37.8	+ 4	Obesity and hypertrophic arthritis
67	9/11/16	♀	50	59.4	166.8	176	42.0	+20	Paroxysmal tachycardia during paroxysm
67	9/11/16	♀	50	59.4	166.8	85	45.3	+29	Paroxysmal tachycardia during interval
69	9/15/16	♀	18	56.3	161.0	87	37.2	— 2	Metrorrhagia
108	11/16/16	♀	45	56.8	164.0	101	38.5	+ 7	Secondary anemia
109	11/17/16	♀	32	46.0	158.2	93	38.6	+ 6	Psychoneurosis
119	12/ 5/16	♀	22	62.3	165.5	96	40.5	+ 9	Neurasthenia
122	12/10/16	♀	31	75.5	175.0	82	39.0	+ 7	Acromegaly, inactive
124	12/19/16	♀	40	67.5	168.0	91	38.9	+ 8	Phlebitis, pelvic inflammatory (subacute), glycosuria
158	3/14/17	♀	20	45.0	163.5	77	38.8	+ 5	Irritable heart
94	10/28/16	♀	78	69.0	163.4	68	36.9	+12	Psoriasis

A more interesting collection of controls is shown in Table 2. This comprises cases with thyroid enlargement, but with no clear cut clinical evidence of thyrotoxicosis. The size and character of the goiter are indicated in the table, and under "Remarks," a statement of the general nature of the case is given. Of these seventeen cases, only two varied more than 10 per cent. from the standard (Nos. 91 and 92). Both these patients had tachycardia, and although very atypical, these may yet have been cases of mild exophthalmic goiter. In our first paper[2] we showed diagrammatically that the elevation in metabolism in thyrotoxicosis runs essentially parallel to the clinical evidence of intoxication. This table shows the corollary that patients with thyroid tumors, but with no definite clinical evidence of hyperthyroidism have no increase in their metabolism. In these seventeen

cases we have been able to secure follow-up data in only seven, but none of these seven have clinically developed any indication of exophthalmic goiter.

Differential Diagnosis. — Soon after the work on our series of exophthalmic goiter cases was started, we began to receive requests from clinicians for basal metabolism determinations for purposes of differential diagnosis in cases presenting suggestive symptoms. Such a group of cases is shown in Table 3. It will be worth while to spend a little time examining these.

Thirty-three cases are included in this table. Of these, twelve (Nos. 35, 46, 73, 74, 75, 80, 81, 103, 118, 146, 155 and 127) showed a variation of not more than 10 per cent. from the standard. Seven of these twelve patients have been seen or heard from this year, and none of them has developed exophthalmic goiter.

One case (No. 65) in which it was thought that prolonged irradiation might have produced hypothyroidism, showed a result 13 per cent. below the standard. This figure is somewhat suggestive of hypothyroidism, no doubt, but the patient, when seen this year, presented no clinical evidence of that condition.

Only three cases of this group showed a rise of more than 40 per cent. One of these (No. 159) was one of recurrent thyroid carcinoma. The metabolism result is interesting inasmuch as the only other thyroid carcinoma we have studied showed a reduction from the normal.[22] The next highest metabolism in this group is that of Case 147. This patient had a colloid goiter with suggestive symptoms. Unfortunately, in neither of these patients were we able to secure follow-up data. Case 112 is quite striking, for when first seen, no goiter or eye signs were present, but he had suggestive symptoms and the metabolism was 44 per cent. above normal. His later history shows that subsequently he developed true exophthalmic goiter.

Of the remaining seventeen cases showing a rise of anywhere between 10 and 40 per cent. above normal, eight have been lost. Four have subsequently developed exophthalmic goiter (Nos. 26, 84, 136 and 152. Two patients are now in good health (Nos. 116 and 153); one case (No. 78) seems to be rather of the effort syndrome class and two cases still remain in the doubtful class (Nos. 27 and 149).

We believe that our Tables 2 and 3 illustrate clearly the importance of metabolism determinations for purposes of differential diagnosis in cases of obscure thyroid disease. Table 2 shows that for the

22. Means, J. H., and Aub, J. C.: Basal Metabolism in Hypothyroidism Arch. Int. Med. **24**:404 (Oct.) 1919.

TABLE 2.—METABOLISM DATA. PATIENTS WITH ENLARGED THYROIDS BUT WITHOUT CLINICAL EVIDENCE OF HYPERTHYROIDISM

No.	Date	Sex	Age	Weight, Kg.	Height, Cm.	Pulse	Calories per Square Meter and Hour	Percentile Variation from Standard	Thyroid			Duration of Goiter	Remarks	Patient's Condition in Spring of 1919
									Degree Enlargement	Character	Bruit			
13	3/27/15	♀	30	56.0	158.0	82	40.0	+10	++	Soft, smooth, symmetrical	0	10 years	Symptoms of toxemia at onset; perfectly well for several years	Remained in good health; has married and had twins
15	4/ 9/15	♀	14	37.5	150.0	81	44.5	+ 3	+	Soft, smooth, symmetrical	0	2 years	In good health.....	No information
	9/28/16		15	41.0	154.0	88	43.3	+ 1	+	Soft, smooth, symmetrical	0	.....	In good health.....	
	1/13/17		16	42.5	155.8	87	44.5	+ 3	0	.....	0	.....	In good health.....	
24	6/ 2/15	♀	25	52.0	169.0	90	38.2	+ 3	+	Soft, smooth, symmetrical	0	3½ years	Well but easily fatigued.....	About the same
61	6/14/16	♀	21	64.0	155.4	67	36.6	0	..	Asymmetrical, irregular goiter, probably multiple cysts	0	1 year	Symptoms of toxemia at onset; none now after course of roentgen ray	No information
70	9/16/16	♀	20	49.8	158.2	82	36.5	— 1	+	Soft, smooth, symmetrical	0	2 years	Slightly nervous; eyes somewhat prominent	Appears neurotic rather than thyrotoxic
76	9/25/16	♀	43	68.0	167.5	87	33.3	— 7	++	Firm, smooth, asymmetrical	0	2 years	Marked psychoneurosis	No information
82	10/ 4/16	♀	30	67.0	172.0	77	39.7	+ 9	++	Soft, smooth, symmetrical	0	6 years	Slight toxemia in past, well now following course of roentgen ray	No information
85	10/12/16	♀	35	47.3	160.0	76	37.6	+ 3	+++	Soft, smooth, symmetrical	0	10 years	Well but easily fatigued.....	No information
90	10/18/16	♀	22	54.7	158.0	76	38.8	+ 5	++	Soft, smooth, symmetrical	+	6 months	Toxemia in past, clearing up on course of roentgen ray	No information
91	10/20/16	♀	34	57.5	163.0	106	42.6	+17	++	Soft, smooth, symmetrical	0	24 years?	Marked neurasthenia, nystagmus...	No information
92	10/21/16	♀	20	46.6	157.0	94	41.3	+12	++	Soft, smooth, symmetrical	0	2 years	Debility	Better; no evidence of Graves' disease
98	11/ 3/16	♀	47	60.0	157.5	79	38.2	+ 6	++	Soft, smooth, symmetrical	0	2 years	Nervous in past, clearing up on course of roentgen ray	Goiter the same; no signs of toxemia
132	1/18/17	♀	30	63.0	176.0	64	35.1	— 4	++	Soft, smooth, symmetrical	0	2 years	Some nervousness in past; none now	No information
133	1/18/17	♀	24	45.5	158.0	83	36.5	— 1	+	Soft, smooth, symmetrical	0	24 years?	Somewhat nervous; history of increased sweating	No information
140	2/10/17	♀	22	63.0	163.5	87	40.1	+ 8	+	Soft, smooth, symmetrical	0	15 years	Occasionally nervous; slight tremor	Goiter the same; no signs of toxemia
145	2/20/17	♀	41	57.0	175.0	101	39.6	+10	..	Round, smooth mass in left lobe size of pigeon's egg; probably cyst	0	15 years	In good health.....	Goiter just as before; no signs of toxemia
150	3/ 4/17	♀	15	51.5	160.0	85	38.5	—10	..	Hard, round mass in isthmus size of a grape	0	15 years	Slight suggestion of myxedema....	No information

TABLE 3.—METABOLISM DATA. BORDERLINE CASES

No.	Date	Sex	Age	Weight, Kg.	Height, Cm.	Pulse	Calories per Square Meter and Hour	Percentile Variation from Standard	Remarks	Patient's Condition in Spring of 1919
9	3/13/15	♀	51	58.2	169.0	133	47.2	+35	Tachycardia of unknown origin	No information
26	6/22/15	♀	33	60.0	158.0	97	44.9	+23	Mitral disease plus suggestive symptoms	Definitely
	4/ 9/19		37	59.5		107	55.5	+52	Slight but definite signs of thyrotoxicosis	Slightly thyrotoxic
27	7/ 8/15	♀	30	50.3	151.0	59	42.6	+17	Full thyroid; slightly suggestive symptoms	Not much evidence of Graves' disease; asthma her chief trouble
	1/20/17		31	51.5		81	44.6	+22		
35	10/21/15	♀	24	43.0	158.8	99	36.0	− 1	Slight eye signs; no thyroid enlargement or toxic symptoms	No information
46	12/14/15	♂	18	56.0	173.0	99	45.0	+10	Tachycardia of unknown origin	No definite evidence of Graves' disease
65	8/28/16	♀	46	67.0	165.0	87	31.3	−13	Prolonged irradiation; ? of hypothyroidism	No evidence of throid disease
73	9/20/16	♀	37	63.0	154.0	89	38.7	+ 6	Very slight fullness of thyroid, eye signs and toxic symptoms	No information
74	9/21/16	♀	36	37.5	155.5	84	34.9	− 4	Postoperative Graves'; slight recurrence of symptoms	Essentially normal
	4/ 7/19		39	37.0		82	36.5	+ 1	Improved; slight tremor; slight nervousness; otherwise no evidence of thyrotoxicosis	
75	4/22/16	♀	29	61.5	162.5	90	38.7	+ 5	Slight fullness of thyroid; very mild symptoms	Normal
78	4/27/16	♂	22	55.4	171.0	89	51.1	+29	Slight fullness of thyroid; very mild symptoms	Seems to fall best in class of "effort syndrome"
	4/29/16		22	55.4		72	45.0	+14		
80	4/29/16	♀	21	58.9	149.0	113	38.6	+ 4	Prolonged irradiation; atypical symptoms now	In good health
81	10/ 3/16	♂	22	60.2	171.0	90	43.5	+10	Full thyroid; slight symptoms	No information
84	10/10/16	♀	24	49.2	161.3	88	44.3	+20	Slight enlargement of thyroid, and somewhat atypical symptoms	Picture of very mild Graves' disease
	2/12/17		24	49.3		86	43.6	+18		
108	11/10/16	♀	15	41.0	156.5	126	43.1	0	Slight fullness of thyroid; suggestive symptoms	No evidence of Graves' disease; moderately neurotic
104	11/11/16	♀	53	69.9	161.8	83	40.1	+15	Intrathoracic goiter	No information
	2/ 8/17		53	66.5		79	37.9	+ 8		
112	11/21/16	♂	50	54.3	169.5	104	54.1	+44	No eye signs or goiter but very suggestive symptoms	Subsequently developed true Graves' disease
115	11/24/16	♀	26	58.4	169.0	88	41.3	+12	Incipient phthisis	No information
116	11/25/16	♀	65	42.0	156.0	133	44.6	+31	Colloid goiter; ? hyperthyroidism	In good health
118	12/ 1/16	♀	36	51.6	167.0	88	39.0	+ 7	Full thyroid and sugestive symptoms	No information
105	11/12/16	♀	43	55.5	157.0	99	43.9	+22	Enlarged thyroid and atypical symptoms	No information
134	1/19/17	♀	36	69.0	170.0	103	43.3	+19	Chronic alcoholism with suggestive symptoms	No information
136	1/29/17	♀	30	55.5	156.0	104	46.9	+28	Enlarged thyroid; suggestive symptoms	Probably had mild attack of Graves' disease in interim
	4/12/19		32	58.0		88	45.9	+26	Improved; five roentgen ray treatments; no evidence of hyperthyroidism now	
146	2/21/17	♀	34	60.3	171.0	89	36.8	+ 1	Enlarged thyroid; suggestive symptoms	No information
147	2/22/17	♀	51	41.3	152.0	90	54.3	+55	Colloid goiter and suggestive symptoms	No information
	2/26/17		51	41.3		98	58.8	+54		
149	2/24/17	♀	44	50.5	162.5	106	49.3	+37	Suggestive symptoms; no eye signs or goiter	Symptoms about as before
152	3/ 7/17	♂	39	70.5	179.0	99	51.4	+30	Suggestive symptoms	Developed true Graves' disease; better now
153	3/ 9/17	♀	21	55.0	172.0	93	43.9	+19	Full thyroid; no symptoms	Perfectly well
154	3/10/17	♀	58	58.3	159.0	94	40.0	+14	Postoperative Graves' disease	No information
155	3/10/17	♂	49	70.0	166.0	89	41.9	+ 9	Marked exophthalmos; no goiter or symptoms	Exophthalmos persists; no other signs of Graves' disease
157	3/13/17	♀	20	56.9	169.0	104	49.5	+34	Full thyroid; no symptoms	No information
159	3/15/17	♂	66	59.0	167.5	102	57.1	+56	Recurrent carcinoma of thyroid	No information
162	4/ 7/17	♀	53	46.5	162.5	89	38.8	+11	Tachycardia of unknown origin	No information
127	1/11/17	♀	31	55.0	178.0	105	38.3	+ 4	Neurasthenia	About the same

most part patients with goiters, but without clinical signs of thyrotoxicosis, have a normal metabolism, and that, furthermore, such cases do not subsequently become toxic. The metabolism determination, therefore, seems to be an excellent means of differentiating toxic and nontoxic goiters. Table 3 indicates that in cases with suggestive symptoms those patients with a normal metabolism do not subsequently develop exophthalmic goiter, while those with an elevation oftentimes do. In this class of cases, therefore, the metabolism determination appears to differentiate between true hyperthyroidism and simple neurasthenia, and makes possible a far earlier diagnosis of exophthalmic goiter than would the clinical picture alone.

Exophthalmic Goiter.—The data of our exophthalmic goiter series are presented in Tables 4, 5 and 6. It will be well to give short histories of these cases, fifty-five in number. The physical findings in each case at the time our first observation was made are indicated by plus marks, one meaning slight, two moderate, three marked. The statement as to the toxicity at the head of each history is based on the clinical impressions, not on the metabolism findings. For all dates the reader is referred to the several tables.

Table 4 shows the results obtained in fifteen cases in which the patients received essentially no treatment except with the roentgen ray, either alone or combined with rest. This table includes:

Case 10.—Mrs. M. J. M. (E. M. 200812, X.Ray 306). Duration, six months. Very toxic. Eye signs + +. Tremor + +. Thyroid moderately enlarged, hard; loud bruit.

After ten roentgen-ray treatments she showed no improvement, objectively, in her metabolism, or in her pulse rate. She thought she felt better, but she gained no weight. She died (Oct. 3, 1917) sixteen months after her last metabolism determination, presumably of exophthalmic goiter.

Case 12.—Mrs. T. W. (E. M. 200595, X.Ray 703). Duration eight years. Slightly toxic. Eye signs, none. Tremor +. Thyroid moderately enlarged, hard; faint bruit; definite myocarditis.

A somewhat atypical case of long standing goiter which, according to the history, had only recently become toxic; for some reason when first seen had been receiving a course of thyroid extract. She presented the picture of mild hyperthyroidism, but the metabolism was elevated 71 per cent. After cessation of thyroid and the administration of quinin hydrobromid, it dropped to 49 per cent., while her pulse dropped from 104 to 80. After six roentgen-ray treatments there was essentially no change in the metabolism and a slight rise in pulse and weight. She was seen this year and did not appear toxic, although the goiter persists. Myocardial insufficiency seemed the chief trouble. A metabolism determination was not obtained.

Case 21.—Miss J. D. (E. M. 201753, X.Ray 519). Duration, two months. Moderately toxic. Eye signs +. Tremor + + +. Thyroid moderately enlarged; loud bruit.

After five roentgen ray treatments she showed a very striking improvement, fall in metabolism and pulse and gain in weight. She died December, 1917. The cause of death could not be learned.

CASE 25.—Mrs. A. L. (E. M. 202294, X.Ray 278). Duration, four months. Moderately toxic. Eye signs, none. Tremor +. Thyroid slightly enlarged, soft; bruit very loud. She showed a fall in metabolism and pulse rate and a gain in weight after four treatments, but no immediate further improvement after three additional treatments. When seen this year she did not appear to be toxic and her symptoms seemed referable to myocarditis. There was no longer any thyroid enlargement, and no eye sign or tremor.

CASE 33.—Mr. B. S. (E. M. 204683, X.Ray 591). Duration, two years. Moderately toxic. Eye signs +. Tremor + +. Thyroid moderately enlarged, soft; bruit + +.

He recovered completely after no other treatment than six roentgen-ray exposures, and he has remained well for over two years doing full work. His last metabolism figure was 14 per cent. below normal, but he presented no clinical signs of myxedema.

CASE 48.—Mrs. E. N. (E. M. 205776, X.Ray 693). Duration, four and one half years. Very toxic. Eye signs + + +. Tremor + +. Thyroid moderately and asymetrically enlarged. Loud bruit.

After thirteen roentgen-ray treatments she has shown a marked improvement, fall in metabolism and pulse. When seen this year she showed slight exophthalmos, but no sign of intoxication. She had become very obese.

CASE 53.—Mr. R. S. (E. M. 206770, X.Ray 729). Duration, three weeks. Moderately toxic. Eye signs + + +. Tremor + + +. Thyroid slightly and symmetrically enlarged, soft. Loud bruit.

He showed essentially no change after seven treatments, but a year later, without further treatment, he showed a marked improvement, fall in metabolism and pulse rate, and gain in weight. He has not been seen this year, but writes that he was accepted for the U. S. Army, went overseas with his organization and has now been discharged and is working in a shipyard.

CASE 66.—Miss E. C. C. (O. P. D. 306686, X.Ray 888). Duration, two years. Moderately toxic. Eye sign +. Tremor +. Thyroid slightly and symmetrically enlarged, rather hard. Moderate bruit.

She had only roentgen-ray treatment. After eleven exposures she had recovered completely. When seen this year she presented no evidence of intoxication and had a normal metabolism. She was working to full capacity.

CASE 107.—Mrs. R. M. (O. P. D. 255857, roentgen ray 964). Duration, three years. Slightly toxic. Eye signs +. Tremor +. Thyroid slight; hard, enlargement of the right lobe. Slight bruit. This patient had had a hemithyroidectomy two years before our first observation, with recurrence of symptoms recently.

She grew distinctly worse after four roentgen-ray treatments. Her present condition has not been learned.

CASE 110.—Miss E. M. (E. M. 211726, X.Ray 1011). Duration, five months. Slightly toxic. Eye signs +. Tremors +. Thyroid slight, soft, symmetrical enlargement. Moderate bruit.

She showed no fall in metabolism on rest alone and then recovered after six roentgen-ray treatments. When seen this year she showed very slight tremor and slightest fullness of the thyroid. Her metabolism was just above normal and she was working to full capacity.

CASE 111.—Mrs. S. S. (E. M. 211757, X.Ray 1012). Duration, two months. Very toxic. Eye signs negative. Tremor + + +. Thyroid moderate soft, symmetrical enlargement. Loud bruit.

After thirteen roentgen-ray treatments she has had a marked fall in metabolism and pulse rate, and a good gain in weight. When seen this year she was clinically improved. She was still toxic, but all signs and symptoms were less marked. She was doing her own housework.

TABLE 4.—METABOLISM DATA. EXOPHTHALMIC GOITER. ROENTGEN-RAY SERIES

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Percentile Variation from Standard	Roentgen Ray Treatments No.	Progress Judged Clinically: Subjectively	Progress Judged Clinically: Objectively	Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
No. 10	3/14/15	68.5	127	59.0	+68	0	.....	.....	A 2 days	
Mrs. M. J. M.	3/20/15	....	119	58.7	+68	0	Same	Same	A	On course of opium since last observation
50 years	4/ 2/15	....	108	58.1	+52	1	Improved	Worse	A	On quinin hydrobromid since last observation
157 Cm.	5/18/16	57.2	127	65.7	+88	9	Improved	Same	C	Doing considerable house work for year; appearance unchanged
No. 12	3/26/15	40.0	104	61.5	+71	0	.....	.....	D	Had been taking thyroid extract; discontinued
Mrs. T. W.	4/17/15	....	80	53.7	+49	0	Same	Same	D	On quinin hydrobromid since last observation; discontinued
41 years										
154.5 Cm.	12/14/16	43.9	96	52.6	+46	6	Improved	Same	D	Goiter smaller
No. 21	5/19/15	45.0	77	54.9	+50	0	.....	.....	A 2 weeks	
Miss J. D.	6/ 3/16	....	81	55.8	+53	1	Improved	Improved	A	
37 years	6/26/15	....	85	54.9	+50	2	Improved	Improved	A	Goiter smaller; much less nervous
164 Cm.	1/31/17	63.2	67	41.3	+13	2	Almost well	Almost well	D	Working for over a year
No. 25	6/ 8/15	50.5	117	66.8	+83	0	.....	.....	A 3 days	
Mrs. A. L.	12/12/16	56.6	106	58.7	+61	4	Improved	Improved	D	
34 years	5/ 2/17	58.2	113	59.5	+63	3	Improved	Improved	D	Feels and looks much better than last year
153 Cm.										
	10/12/15	50.0	103	70.3	+78	0	.....	.....	A 1 day	
No. 33	6/ 5/16	52.7	96	59.6	+51	4	Improved	Improved	C	Better; tremor most troublesome symptom, interferes with work; barber
Mr. B. S.										
24 years	11/23/16	57.0	65	45.2	+14	2	Improved	Well	D	Practically well; tremor nearly gone
169.5 Cm.	2/ 1/17	60.0	73	39.8	+ 1	0	Well	Well	D	Perfectly well; working
	5/ 5/19	59.0	56	34.1	−14	0	Well	Well	D	Working since last observation
	1/ 1/16	52.0	137	66.3	+82	0	.....	.....	A 2 weeks	
	1/21/16	53.3	123	58.8	+61	1	Improved	Improved	A	
No. 48	2/ 2/16	53.5	118	59.0	+62	0	Improved	Improved	A	Less tremor; less exophthalmos
Mrs. E. N.	6/ 9/16	60.0	102	58.9	+61	1	Same	Same	C	
30 years	10/16/16	69.5	120	59.5	+63	0	Same	Improved	D	Signs of thyrotoxicosis much less marked; some myocardial damage
168 Cm.	1/ 8/17	68.0	96	56.1	+54	4	Same	Improved	D	
	4/26/17	74.3	93	46.0	+28	4	Improved	Improved	D	
	4/14/19	90.0	97	46.3	+27	3	Well	Well	D	Leeding normal life for 2 years
	5/13/19	87.0	88	45.8	+25	0	Well	Well	D	
	2/16/16	64.5	100	58.5	+48	0	.....	.....	A 2 days	
No. 53	5/17/16	61.0	98	62.1	+57	5	Same	Same	C	
Mr. R. S.	11/20/16	65.5	96	63.1	+60	2	Improved	Same	C	
21 years	2/13/17	63.0	92	59.0	+49	0	Well	Same	C	Eye signs less marked than a year ago; not objectively nervous now
171.5 Cm.	12/12/17	66.0	70	44.6	+13	0	.....	.....	D	

No. 66	8/29/16	48.2	118	32.6	+42	0	.....	.....	D	
Miss E. C. C.	12/ 2/16	49.6	118	49.2	+33	4	Improved	Improved	D	
27 years	2/24/17	50.0	104	41.8	+13	2	Improved	Improved	D	Teaching school; almost no tremor
174.5 Cm.	4/ 7/17	49.0	104	47.3	+28	1	Same	Same	D	Thyroid smaller; less bruit
	4/12/19	49.0	80	34.6	— 6	4	Well	Well	D	No eye signs; no tremor; no thyroid enlargement
No. 107	11/16/16	45.0	...	49.3	+41	0	.....	.....	D	
Mrs. R. M.	1/27/17	45.5	81	42.5	+21	3	Improved	Well	D	Leading normal life; appears and feels well
51 years	4/ 5/17	49.0	106	53.8	+54	1	Worse	Worse	D	Recurrence of symptoms following overwork
156 Cm.										
	11/19/16	56.8	96	49.0	+34	0	.....	.....	A 4 days	Quinin hydrobromid for last ten days
	11/24/16	56.6	112	51.7	+42	0	Same	Improved	A	
No. 110	12/ 3/16	54.7	108	49.1	+35	1	Same	Improved	A	
Miss E. M.	12/18/16	56.8	119	51.7	+42	0	Improved	Improved	A	
39 years	1/30/17	61.0	105	48.9	+34	2	Improved	Same	C	Thinks she is much better; still looks toxic
157.5 Cm.	3/ 8/17	64.7	91	42.8	+17	1	Improved	Improved	C	Appears less toxic
	4/ 9/17	65.5	84	36.3	— 1	2	Almost well	Improved	D	Been back at work for six weeks
	5/ 7/19	66.5	78	41.3	+15	0	Well	Well	D	
	11/19/16	39.0	121	65.4	+87	0	.....	.....	A 2 days	Extreme nervousness
No. 111	11/26/16	38.5	129	64.1	+83	0	Improved	Same	A	
Mrs. S. S.	12/ 5/16	37.1	114	55.0	+57	1	Improved	Improved	A	Less nervous
55 years	1/10/17	40.0	140	65.6	+87	1	Improved	Improved	C	
151.2 Cm.	3/ 8/17	41.0	141	64.7	+85	2	Improved	Same	C	
	4/15/19	48.5	100	44.0	+26	9	Improved	Improved	D	Very slight tremor; thyroid barely perceptible
No. 113	11/22/16	58.0	153	65.6	+77	0	.....	.....	D	
Mrs. B. M. T.	1/25/17	55.0	116	54.6	+48	2	Same	Improved	D	Acute infection for last two weeks
23 years	3/12/17	54.5	110	51.6	+39	2	Same	Improved	A 1 week	
155.8 Cm.	4/29/17	55.2	133	54.3	+47	0	Same	Same	A 1 week	Had diphtheria between this and preceding observation
No. 120	12/ 7/16	53.6	128	60.2	+67	0	.....	.....	D	
Mrs. I. K.	12/22/16	49.5	130	61.6	+71	0	Same	Same	C	
45 years	1/31/17	50.5	112	56.2	+56	2	Improved	Same	D	Exophthalmos increasing
160 Cm.	3/29/17	58.5	114	58.4	+48	2	Improved	Improved	D	Seems less toxic but eye signs are increasing and thyroid enlarging
	12/14/16	48.0	157	70.0	+89	0	.....	.....	C	
	12/20/16	49.0	153	64.2	+74	0	Same	Same	A 1 day	
	1/ 9/17	42.3	112	49.7	+34	1	Improved	Improved	A	
No. 123	1/13/17	43.0	118	51.9	+40	0	Improved	Improved	A	
Mrs. C. Mv.	1/21/17	43.6	127	57.5	+55	0	Worse	Worse	A	
29 years	2/ 1/17	43.9	122	58.6	+58	1	.....	.....	A	
152.5 Cm.	3/ 3/17	43.5	128	64.3	+74	0	Same	Same	C	
	4/24/17	51.0	125	68.9	+73	3	Improved	Improved	D	Much better; looking after husband and two children
	4/26/18	56.0	122	60.5	+66	1				
	5/ 7/19	55.0	111	50.6	+39	0	Improved	Same	D	
	1/28/17	53.2	122	50.6	+39	0	.....	.....	A 11 days	Quinin hydrobromid for six months
No. 125	2/ 7/17	53.7	106	44.4	+22	0	Improved	Improved	A	
Mrs. V. M. D.	2/15/17	53.9	108	46.9	+28	0	Improved	Improved	A	Less exophthalmos
39 years	3/ 9/17	57.5	119	53.5	+47	0	Improved	Same	C	
164.5 Cm.	4/ 5/17	58.1	108	46.5	+27	1	Worse	Same	C	Doing light housework
	1/30/18	56.0	116	45.1	+25	6				
	5/10/19	65.5	104	57.5	+ 4	0	Well	Well	D	Has had a healthy child since last observation

Case 113.—Mrs. B. M. T. (E. M. 213651, X.Ray 1015). Duration, three years. Moderately toxic. Eye signs +. Tremor + +. Thyroid moderate, soft, symmetrical enlargement. Faint bruit.

She improved somewhat after four roentgen-ray treatments but died later, the date and cause of death being unknown to us.

Case 120.—Mrs. I. K. (O. P. D. 315898, X.Ray 1029). Duration, one year. Moderately toxic. Eye signs + + +. Tremor + + +. No visible enlargement of thyroid.

She showed some improvement after four roentgen-ray treatments. Subsequently she has remained in fairly good health, but both eyes have had to be enucleated because of extreme exophthalmos.

Case 123.—Mrs. C. M. (E. M. 212328, X.Ray 1020). Duration, eight years. Very toxic. Eye signs + + +. Tremor + + +. Thyroid marked, soft, symmetrical enlargement. Loud bruit.

After six roentgen-ray treatments she showed a definite improvement; fall in metabolism and pulse and gain in weight. When seen this year she was clinically improved. The exophthalmos persists. Slight tremor was present. The goiter was smaller. She was still somewhat toxic but was working to usual capacity.

Case 135.—Mrs. V. M. D. (W. M. 212958, X.Ray 872). Duration, one year. Slightly toxic. Eye signs + + +. Tremor +. Thyroid slight, soft symmetrical enlargement. Faint bruit.

She recovered after seven treatments. When seen this year, except for slight exophthalmos and a persistent tachycardia she showed no signs or symptoms of exophthalmic goiter. Her metabolism was normal, and she was caring for her family and nursing her baby.

In Table 5 are collected the data obtained in sixteen cases before and after partial thyroidectomy.

Case 3.—Mrs. L. S. (W. M. and W. S. 197641). Duration, four years. Very toxic. Eye signs + +. Tremor + +. Thyroid moderate, soft symmetrical enlargement. Loud bruit.

One year and one half after lobectomy she showed a fall in metabolism and a gain in weight. No change occurred in her pulse rate. Her condition this year could not be learned.

Case 16.—Mr. S. T. (W. M. and W. S. 201372). Duration, one year. Moderately toxic. Eye signs + +. Tremor + + +. Thyroid, moderate, soft symmetrical enlargement.

Two years after operation he showed a higher metabolism than he did before. Essentially, no change in pulse rate and a slight gain in weight. His condition this year could not be learned.

Case 51.—Mr. W. W. H. Duration, eight months. Slightly toxic. Eye signs +. Tremor +. Thyroid, slight fullness; faint bruit. He gave a history of no improvement after six roentgen-ray treatments. After lobectomy at the Mayo clinic he gained weight, had a normal metabolism and a slower pulse. Later he had a slight return of toxemia. He has not been seen this year, but writes that he is quite well.

Case 71.—Mrs. H. R. (E. M. and W. S. 210587, X.Ray 794). Duration eighteen months. Moderately toxic. Eye signs +. Tremor +. Thyroid, moderate, soft symmetrical enlargement.

She gave a history of no improvement after eight roentgen-ray treatments. This was before coming under our observation. She showed a striking fall in metabolism and pulse rate immediately after operation and later a rise. This year her metabolism is still 22 per cent. above normal, but she has gained weight, has no tachycardia and appears to be well. There is still slight exophthalmos. She is following her usual occupation.

CASE 83.—Mr. W. H. (W. M. and W. S. 210852). Duration, one year. Very toxic. Eye signs + + +. Tremor +. Thyroid, moderately enlarged. Faint bruit.

When first seen he was still toxic in spite of a ligation done at the Mayo Clinic. He showed a striking improvement after lobectomy and had a normal metabolism and pulse rate one month after operation. His condition this year was not learned.

CASE 88.—Miss C. P. (E. M. and W. S. 211054, X.Ray 879). Duration, one year. Very toxic. Eye signs + + +. Tremor + +. Marked, soft symmetrical enlargement of thyroid. Loud bruit.

She gave a history of no improvement after four roentgen-ray treatments, but showed a marked improvement after ligation and then grew worse again after lobectomy. This year, however, she is looking and feeling well, and her metabolism is only + 15 per cent. She has been working for two years; a slight exophthalmos remains.

CASE 99.—Miss M. T. P. (W. M. and W. S. 211454, X.Ray 1094). Duration, eleven years. Very toxic. Eye signs + + +. Tremor + + +. Thyroid, marked asymmetric enlargement. Loud bruit.

This patient also reported no improvement after eight roentgen-ray treatments. She showed an increase in toxemia following lobectomy, but later a gradual improvement under roentgen-ray treatment. When seen this year she still had a slight exophthalmos, slight fullness of the left lobe of the thyroid, with bruit, but other signs and symptoms of thyrotoxicosis were practically absent. Her metabolism was decreased and she had been working to full capacity for one year and one half.

CASE 106.—Mrs. N. M. (E. M. and W. S. 211553). Duration, two years. Slightly toxic. Eye signs, none. Tremor +. Thyroid, moderate, hard, asymmetrical enlargement. No bruit.

She apparently became entirely normal within four months after lobectomy. This year she was clinically well, but her metabolism was + 24 per cent.

CASE 117.—Miss V. R. (W. M. and W. S. 211801). Duration, two years. Slightly toxic. Eye signs +. Tremor + +. Thyroid, slight soft symmetrical enlargement. Faint bruit.

After operation she showed an immediate decrease followed by an increase in toxemia. However, she writes this year that she is in excellent health. She has been married and is doing her own housework.

CASE 125.—Miss M. D. (E. M. and W. S. 212305). Duration, one and one half years. Very toxic. Eye signs, +. Tremors, + + +. Thyroid, moderate, hard, symmetrical enlargement. Loud bruit.

She had had a ligation before coming under our observation. She showed a marked fall in pulse rate and metabolism on rest in bed, and a continued gradual improvement after a ligation and lobectomy. When seen this year she had a slight exophthalmos and a hard mass in the isthmus of the thyroid, the size of a pigeon's egg; no bruit. There was no evidence of thyrotoxicosis. Metabolism was decreased and she had been working for two years as a domestic.

CASE 126.—Mrs. M. L. (W. M. and W. S. 212598). Duration, eighteen months. Slightly toxic. Eye signs, +. Tremor, +. Thyroid, slight soft symmetrical enlargement. Faint bruit.

She had had nine roentgen-ray treatments before coming under our observation. She showed a return of the metabolism to normal, a normal pulse rate and a gain in weight after lobectomy. She died subsequently. We have been unable to learn the date and cause of death.

CASE 129.—Mr. W. E. R. (W. M. and W. S. 212711). Duration, one year. Slightly toxic. Eye signs, none. Tremor + +. Thyroid, slight fullness. No bruit.

TABLE 5.—METABOLISM DATA. EXOPHTHALMIC GOITER. SURGICAL SERIES

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Percentile Variation from Standard	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
						Subjectively	Objectively		
	10/ 8/14	42.0	104	65.6	+80	.....	.....	A 3 weeks	Three roentgen ray treatments before coming under observation
No. 3	10/10/14	42.0	102	63.1	+73	Same	Same	A	One roentgen ray treatment
Mrs. L. S.	11/ 6/14	39.2	104	59.0	+62	Improved	Improved	A	Lobectomy Oct. 16, 1914
35 years	6/ 6/16	53.0	108	54.5	+49	Improved	Improved	D	Much better; all signs and symptoms greatly diminished; working
157 Cm.									
No. 16						.....	.....	A 1 day	
Mr. S. T.	4/19/15	62.7	100	51.4	+30				
23 years	3/31/17	67.0	96	57.1	+45	Same	Improved	D	Lobectomy April 20, 1915
168 Cm.									
No. 51	2/ 8/16	54.6	108	55.2	+40	.....	.....	C	Six roentgen ray treatments before coming under observation
Mr. W. W. H.									
33 years	6/20/16	58.0	80	40.4	+ 2	Improved	Well	C	Lobectomy May 19, 1916, at Mayo Clinic
174.5 Cm.	12/22/16	61.5	96	47.0	+19	Worse	Worse	D	Back at work in banking business
	9/19/16	68.0	113	49.6	+36	.....	.....	A 1 day	Had eight roentgen ray treatments before coming under observation, without improvement
	9/23/16	67.6	101	51.1	+40	.....	.....	A	
	10/ 2/16	65.9	88	42.1	+15	Improved	Improved	A	Lobectomy Sept. 25, 1916
No. 71	10/31/16	69.5	122	49.8	+36	Improved	Improved	C	
Mrs. H. R.	11/14/16	70.5	113	49.4	+35	Improved	Improved	D	
37 years	12/12/16	70.9	101	46.1	+26	Worse	Same	D	
166.5 Cm.	2/ 3/17	72.5	104	45.5	+25	Same	Improved	D	
	4/11/17	73.5	93	43.8	+20	Well	Improved	D	
	4/ 1/19	77.5	88	44.8	+23	Well	Well	D	
	4/29/19	76.0	80	44.5	+22	Well	Well	D	
No. 83	10/ 5/16	49.9	127	61.7	+56	.....	.....	A 3 days	Ligation at Mayo Clinic July, 1916, superior arteries
Mr. W. H.	10/ 9/16	52.0	96	53.7	+36	.....	.....	A	
22 years	10/27/16	45.5	97	51.5	+30	Improved	Improved	A	Lobectomy Oct. 16, 1916
160 Cm.	11/18/16	43.6	81	42.8	+ 8	Improved	Improved	C	

	10/14/16	54.7	144	64.1	+73	.....	.....	A 3 days	Had four roentgen ray treatments before coming under observation, without improvement
	10/18/16	54.7	141	57.1	+54	.....	.....	A	
	10/26/16	51.8	143	56.1	+52	Improved	Same	A	
No. 88	11/11/16	51.0	124	44.3	+20	Improved	Improved	A	Ligation Nov. 2, 1916
Miss C. P.	11/29/16	52.3	129	47.3	+28	Improved	Improved	A	Lobectomy Nov. 17, 1916
22 years	12/11/16	51.1	127	47.8	+29	Improved	Improved	A	All signs and symptoms less marked
161 Cm.	1/17/17	52.5	142	55.3	+49	Improved	Improved	C	
	3/30/17	55.0	116	56.9	+54	Improved	Improved	D	
	11/22/17	54.5	Lost	46.7	+26				
	4/27/19	48.5	90	42.5	+15	Well	Well	D	Exophthalmos nearly gone; no tremor; no thyroid palpable
	11/ 3/16	59.5	112	62.7	+72	.....	.....	A 1 day	Had eight roentgen ray treatments before coming under observation, without improvement
	11/ 7/16	55.8	110	57.5	+58	Same	Same	A	Quinin hydrobromid since last note
	11/15/16	54.5	89	51.7	+42	Improved	Improved	A	
No. 99	12/16/16	49.0	103	50.9	+39	Improved	Improved	A	Lobectomy Nov. 23, 1916
Miss M. T. P.	2/19/17	56.0	119	58.5	+60	Improved	Worse	C	
36 years	2/28/17	59.1	101	55.8	+53	Improved	Improved	C	
170.6 Cm.	4/18/17	61.0	108	53.4	+46	Improved	Improved	C	
	9/13/17	65.0	96	45.3	+24	.....	.....	.....	Four roentgen ray treatments
	3/27/19	59.0	76	45.7	+25	Improved	Well	D	One roentgen ray treatment
	11/14/16	37.4	112	53.9	+50	.....	.....	A 1 week	
No. 106	11/19/16	37.2	107	54.0	+50	Same	Same	A	
Mrs. N. M.	12/10/16	38.0	82	38.4	+ 7	Improved	Improved	A	Lobectomy Nov. 24, 1916
41 years	2/26/17	42.5	77	42.2	+17	Improved	Well	D	
158.5 Cm.	3/30/17	41.2	80	37.9	+ 5	Improved	Hypo.?	D	Some slight suggestion of myxedema
	8/ 5/19	48.0	74	44.7	+24	Well	Well	D	
	11/26/16	46.6	114	53.5	+45	.....	.....	A 6 days	
	12/ 2/16	45.9	110	47.2	+28	Same	Same	A	
	12/15/16	46.8	100	46.3	+25	.....	.....	A	
No. 117	12/27/16	49.6	108	51.3	+39	Improved	Same	A	
Miss V. R.	1/ 2/17	50.3	119	52.1	+41	Improved	Improved	A	
22 years	1/15/17	49.6	103	41.9	+13	Same	Same	A	Lobectomy Jan 6, 1917
168.2 Cm.	1/21/17	49.5	100	44.2	+19	Improved	Improved	A	
	1/30/17	50.7	99	44.5	+20	.....	.....	A	
	2/20/17	52.5	106	46.9	+27	Improved	Improved	C	
	3/25/17	51.0	102	48.6	+31	Improved	Improved	D	
	12/18/16	53.2	133	70.6	+91	.....	.....	A 1 day	Ligation at St. Lukes Hospital, New Bedford, May, 1916
	12/26/16	53.0	99	59.4	+61	.....	.....	A	
	1/11/17	53.0	108	61.1	+65	Improved	Improved	A	One roentgen ray treatment since last observation
No. 125	1/19/17	50.5	91	55.7	+50	Same	Improved	A	
Miss M. D.	1/26/17	51.4	102	51.6	+39	Improved	Same	A	Ligation Jan. 19, 1917
27 years	2/10/17	52.7	96	49.8	+35	Same	Improved	A	Lobectomy Jan. 30, 1917
166.8 Cm.	2/19/17	52.7	85	49.7	+34	Improved	Same	C	
	3/28/17	50.0	79	46.9	+27	Improved	Almost well	C	
	4/26/19	50.0	78	45.5	+23	Improved	Well	D	Working for nearly two years

TABLE 5.—METABOLISM DATA. EXOPHTHALMIC GOITER. SURGICAL SERIES—*Continued*

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Percentile Variation from Standard	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
						Subjectively	Objectively		
No. 126	1/ 7/17	49.3	122	53.5	+47	.....	.....	A 2 days	Had nine roentgen ray treatments before coming under observation
Mrs. M. L.	1/20/17	50.3	105	52.6	+44	Improved	Improved	A	
34 years	2/ 4/17	49.9	96	41.6	+14	Improved	Improved	A	Lobectomy Jan. 23, 1917
160 Cm.	2/11/17	49.3	105	43.4	+19	Improved	Improved	A	
	3/27/17	51.0	100	43.8	+20	Almost well	Almost well	C	
	10/29/17	56.5	76	37.4	+ 2				
No. 129									
Mr. W. E. B.	1/14/17	47.7	145	58.9	+49	.....	.....	A 3 days	
29 years	5/ 7/19	52.5	96	39.8	+ 3	Well	Well	D	Lobectomy Jan. 20, 1917, at private hospital
169.5 Cm.									
	2/ 3/17	58.0	112	67.5	+71	.....	.....	A 1 day	
No. 137	2/16/17	55.0	119	63.5	+61	Improved	Improved	A	Had an acute throat infection since last note and developed auricular fibrillation
Mr. E. T. B.	2/25/17	50.9	96	66.9	+69	Worse	Worse	A	
35 years	3/ 2/17	51.6	102	61.6	+56	Improved	Improved	A	
166.2 Cm.	3/14/17	49.5	87	52.8	+34	Improved	Improved	A	Lobectomy March 5, 1917
	4/ 7/17	58.2	121	65.9	+67	Improved	Improved	C	
	3/29/19	66.0	64	40.9	+ 4	Well	Well	D	Three roentgen ray treatments, spring of 1917
	2/15/17	54.1	104	46.3	+27	.....	.....	A 3 days	Had seven roentgen ray treatments before coming under observation
No. 143	2/18/17	54.1	105	48.1	+32	Same	Same	A	
Miss M. E. H.	3/ 4/17	53.0	107	43.3	+19	.....	.....	A	Lobectomy Feb. 24, 1917
26 years	3/15/17	55.0	100	41.3	+13	Improved	Improved	A	
156 Cm.	4/20/17	53.6	92	46.6	+28	Improved	Improved	C	
	4/ 9/19	54.5	64	32.3	—11	Well	Well	D	Lobectomy June 30, 1917
No. 148	2/23/17	47.0	110	56.2	+52	.....	.....	D	
Miss B. H.	6/25/17	46.0	94	54.1	+46	.....	.....	A	One roentgen treatment
26 years	5/ 1/19	50.5	60	40.9	+10	Well	Well	D	Lobectomy June 28, 1917
161 Cm.									
	3/ 6/17	52.2	117	64.6	+79	.....	.....	A 1 day	
No. 151	3/13/17	52.3	111	59.1	+64	Improved	Same	A	
Mrs. M. E. T.	3/19/17	51.4	102	56.6	+57	.....	.....	A	
46 years	4/ 1/17	49.0	100	48.5	+35	Improved	Improved	A	Lobectomy March 27, 1917
158 Cm.	5/ 9/19	49.0	117	50.3	+40	Improved	Improved	D	

Two years after lobectomy he had a normal metabolism and clinically was well. He was working to full capacity.

CASE 137.—Mr. E. T. B. (E. M. and W. S. 213101). Duration, six years. Moderately toxic. Eye signs +. Tremor + +. Thyroid, moderate soft, symmetrical enlargement. Faint bruit.

He showed little consistent improvement immediately after lobectomy. When seen two years later, he was well, but he had had three roentgen-ray treatments in that time. Slight exophthalmos persisted, but his metabolism was normal and he had been working for nearly two years.

CASE 143.—Miss M. E. H. (W. M. and W. S. 213273). Duration, ten months. Slightly toxic. Eye signs, none. Tremor + +. Thyroid, moderate, soft, symmetrical enlargement. Moderate bruit.

She had had seven roentgen-ray treatments before coming under our observation. She apparently was cured by two successive lobectomies. When seen this year she had no signs or symptoms of exophthalmic goiter. She had a normal metabolism, and had been working for more than one year.

CASE 148.—Miss B. H. (E. M. and W. S. 215081). Duration, two months. Very toxic. Eye signs +. Tremor +. Thyroid moderate, soft symmetrical enlargement. Faint bruit.

When seen this year, two years after operation, she had no signs or symptoms of exophthalmic goiter, except a slight exophthalmos. She had a normal metabolism, and had been working one year.

CASE 151.—Mrs. M. E. T. (W. M. and W. S. 213639). Duration, eight months. Moderately toxic. Eye signs +. Tremor + +. Thyroid, moderate, soft, symmetrical enlargement. Loud bruit.

When seen two years after lobectomy she still had an elevated metabolism and signs and symptoms of a slight thyrotoxicosis. She was doing light housework.

In Table 6 are collected a somewhat miscellaneous group, some in which the series of observations is incomplete, and some that were followed both during the roentgen-ray and the surgical treatments.

CASE 18.—Miss M. A. W. (E. M. 201409). Duration, six years. Slightly toxic. Eye signs +. Tremor, none. Slight thyroid enlargement.

She gave a history of having had a more severe exophthalmic goiter in the past, from which she had recovered. She improved rapidly on a short rest and quinin hydrobromid. She has remained well. She is working at her profession of nursing.

CASE 22.—Miss H. Duration, seven years. Moderately toxic. Eye signs + +. Tremor +. Thyroid, right lobe enlarged. Bruit present.

One observation only was made on this patient. She had a thyrotoxicosis recurring after a lobectomy done seven years before. She also showed an elevation of 43 per cent. in the basal metabolism. Her present condition is not known.

CASE 23.—Mrs. F. G. (E. M. and W. S. 201801, X.Ray 511). Duration, eight years. Very toxic. Eye signs + + +. Tremor + +. Thyroid, marked, hard enlargement. Loud bruit.

She died two days after ligation of the right superior thyroid vessels. The vessels on the left side had been ligated eleven days before.

CASE 32.—Mrs. E. J. S. (E. M. 204549). Duration, three years. Slightly toxic. Eye signs +. Tremor +. Thyroid, slightly and asymmetrically enlarged. No bruit.

This patient appeared clinically to be only slightly toxic, but she had a very high metabolism. When seen five and one half months later, having followed

TABLE 6.—METABOLISM DATA. EXOPHTHALMIC GOITER. MISCELLANEOUS

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Percentile Variation from Standard	Roentgen Ray Treatments No.	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
							Subjectively	Objectively		
No. 18	4/22/15	....	71	39.9	+ 9	0	.....	.....	A 1 week	
Miss M. A. W.	10/23/16	48.0	86	41.5	+14	0	Improved	Improved	C	On quinin hydrobromid
31 years	4/ 2/17	49.5	90	39.4	+ 8	0	Improved	Improved	D	
164 Cm.										
No. 22										
Miss H.	5/23/15	65.5	105	52.1	+43	0	.....	.....	D	Lobectomy in 1906
35 years										
No. 23										
Mrs. F. G.	5/24/15	33.7	121	67.0	+81	1	.....	.....	A 12 days	June 11, 1915, Ligation left superior vessels; June 22, 1915, ligation right superior vessels
29 years										
No. 32										
Mrs. E. J. S.	10/ 7/15	58.0	111	63.1	+73	0	.....	.....	A 5 days	
38 years	3/28/17	55.0	120	68.4	+87	1	Improved	Improved	D	Goiter smaller
163.5 Cm.										
No. 40										
Mrs. D. K. N.	11/ 9/15	55.8	103	47.4	+28	0	.....	.....	A 1 week	
27 years										
163 Cm.										
No. 52										
Miss C. M.	2/10/16	50.0	130	65.3	+76	0	.....	.....	A 6 days	Ligations, November and December, 1913; lobectomy March 2, 1916
22 years										
170 Cm.										
No. 59										
Miss A. M. B.	6/ 5/16	47.5	132	49.1	+36	0	.....	.....	A 4 days	
40 years										
157 Cm.										
No. 62	6/16/16	61.0	117	49.1	+36	4	.....	.....	C	
Mrs. M. A. H.	11/23/16	61.5	112	48.0	+33	5	Improved	Same	C	
40 years	3/29/17	60.0	106	47.7	+32	2	Improved	Same	C	
155.3 Cm.	8/ 7/19	57.0	94	48.6	+35	0	Improved	Improved	D	

No. 68 Mrs. J. B. 35 years 159.2 Cm.	9/12/16	50.5	88	50.6	+39	9	.....	.....	D	
	12/13/16	53.0	90	46.1	+26	2	Improved	Worse	D	
	2/17/17	54.5	81	49.9	+37	3	Worse	Same	A	
	2/26/17	52.4	80	47.7	+31	0	Improved	Improved	Same	
	4/ 8/19	49.5	82	49.9	+37	8	Improved	Improved	D	
No. 72 Miss E. P. 18 years 161 Cm.	9/19/16	51.1	111	49.4	+30	5	.....	.....	D	
	11/28/16	53.5	106	49.5	+30	0	Improved	Improved	D	
No. 77 Mrs. S. I. R. 29 years 154.5 Cm.	9/26/16	53.4	151	54.6	+48	0	.....	.....	A 3 days	
	10/ 7/16	50.0	133	54.5	+47	0	Same	Same	A	
	10/21/16	49.1	124	58.5	+58	0	Improved	Improved	A	Lobectomy Nov. 3, 1916
No. 89 Miss M. S. 23 years 162.5 Cm.	10/14/16	61.0	113	57.1	+54	5	.....	.....	D	
	12/ 4/16	64.0	101	50.1	+35	2	Improved	Same	D	
	2/ 9/17	63.0	110	54.0	+46	3	Same	Improved	D	
	3/26/17	61.0	103	54.1	+46	3	Same	Same	D	Working in shoe factory right along; has done so ever since onset
No. 93 Mrs. A. B. 33 years 163 Cm.	10/27/16	55.2	131	51.0	+40	0	.....	.....	C	
	1/ 7/17	51.9	133	49.9	+37	2	Same	Same	A 6 days	Just recovered from acute tonsillitis
	1/22/17	53.5	129	50.3	+38	1	Same	Same	A	
	2/13/17	56.7	125	49.8	+37	1	Same	Same	A	
	2/24/17	55.5	103	38.4	+ 5	0	Well	Improved	A	Lobectomy Feb. 14, 1917
	3/ 3/17	57.2	99	39.2	+ 7	0	Well	Improved	A	
	3/28/17	58.0	102	38.1	+ 4	0	Weak	Same	D	Doing housework
	2/ 4/18	59.0	98	36.6	0	0				
	4/ 1/19	59.0	88	32.7	— 8	0	Improved	Well	D	
No. 100 Miss E. McH. 41 years 147 Cm.	11/ 4/16	51.1	149	50.6	+41	15	.....	.....	A 3 days	
	11/ 7/16	51.5	140	50.2	+39	0	Same	Same	A	
No. 114 Miss O. S. 41 years 164.8 Cm.	11/23/16	55.0	107	53.0	+47	1	.....	.....	C	
	1/10/17	65.5	76	34.9	— 3	2	Improved	Well	D	
	5/ 3/17	63.0	74	38.0	+ 6	1	Well	Well	D	
	7/ 2/19	60.5	68	34.5	— 4	0	Well	Well	D	
No. 121 Miss M. M. 21 years 152.5 Cm.	12/ 9/16	59.5	126	80.5	+118	0	.....	.....	D	
	12/16/16	57.0	131	77.4	+109	0	.....	.....	A 1 day	
	12/23/16	56.3	117	67.9	+84	0	Improved	Improved	A	
	1/ 6/17	55.5	116	67.9	+84	1	Improved	Improved	A	
	1/12/17	55.0	112	63.5	+72	0	.....	.....	A	
	1/22/17	52.3	108	65.7	+78	0	Improved	Same	A	
	1/31/17	52.3	122	64.2	+74	0	Same	Same	A	
	2/12/17	52.3	117	64.2	+74	0	Improved	Improved	A	
	3/ 5/17	53.2	141	75.1	+103	1	Improved	Same	B	
	3/27/17	56.0	114	66.2	+79	1	Same	Same	B	
	4/13/17	58.7	111	58.5	+58	1	Same	Same	A 2 days	
	4/29/17	58.1	79	42.7	+15	0	Improved	Improved	A	Lobectomy April 16, 1917
	4/10/19	60.5	59	41.1	+11	3	Well	Well	D	

TABLE 6.—METABOLISM DATA. EXOPHTHALMIC GOITER. MISCELLANEOUS—(*Continued*)

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Percentile Variation from Standard	Roentgen Ray Treatments No.	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
							Subjectively	Objectively		
	1/16/17	50.5	125	58.5	+46	0	.....	.....	A 1 day	
No. 130	1/17/17	50.2	120	54.1	+35	0	.....	.....	A	
Miss K. L.	1/22/17	50.3	112	52.0	+30	0	Improved	Improved	A	
17 years	1/30/17	49.5	103	52.5	+31	0	Same	Same	A	
167.7 Cm.	2/ 8/17	50.0	109	50.4	+26	0	Improved	Same	A	
	2/14/17	51.0	107	48.8	+22	0	.....	.....	A	
	4/28/17	56.0	99	51.3	+28	0	Improved	Same	C	Lobectomy Feb. 24, 1917, at Melrose Hospital
	1/16/17	59.0	99	51.9	+42	0	.....	.....	A 3 days	
No. 131	1/22/17	59.5	81	48.6	+23	0	Improved	Improved	A	
Mrs. S. J. G.	2/ 4/17	57.5	97	47.7	+31	0	Improved	Improved	A	
33 years	3/22/17	55.3	96	48.1	+32	1	Same	Same	A	Just been through a bronchopneumonia and after that an acute frontal sinusitis
170 Cm.	4/26/19	61.5	77	44.5	+22	0	Improved	Well	D	Never has had any consistent treatment
No. 138	2/ 5/17	64.5	104	53.7	+36	0	.....	.....	D	Quinin hydrobromid for one week
Mr. C. J.	2/19/17	67.5	102	55.8	+41	0	Same	Same	D	
38 years	4/ 3/17	67.7	101	56.3	+43	0	Improved	Improved	D	
156 Cm.										
No. 139										
Mrs. R. K.	2/ 6/17	58.0	108	55.6	+50	1	.....	.....	D	
23 years	4/12/17	55.0	107	54.6	+48	2	Improved	Same	D	
161.5 Cm.										
No. 144										
Mrs. H.	2/17/17	74.3	113	53.8	+47	0	.....	.....	A 3 days	Lobectomy July, 1914, Peter B. Brigham Hospital
37 years	3/ 7/17	76.0	82	46.4	+27	0	.....	.....	A	
163.7 Cm.										
No. 156										
Theodore D.	3/12/17	28.8	124	65.6	+29	0	.....	.....	A 3 days	
11 years	8/ 2/19	39.0	102	52.7	+15	4	Improved	Improved	D	
147.5 Cm.										
No. 160										
Mrs. K.	3/26/17	57.8	119	62.3	+78	0	.....	.....	A 2 days	
57 years	4/10/17	47.5	130	69.5	+99	1	Worse	Worse	A	Lobectomy April 13, 1917
170 Cm.										
No. 161										
Mrs. C. M.	3/29/17	46.4	126	68.1	+84	0	.....	.....	A 12 days	
26 years	4/ 6/17	45.5	128	61.6	+67	0	Same	Same	A	
165 Cm.	10/ 8/17	51.0	118	61.1	+65	0	.....	.....	A	Lobectomy Oct. 10, 1917

no treatment in the interim, she appeared and felt better, but had a still higher metabolism and pulse rate, and she had lost weight. Her present condition could not be learned.

CASE 40.—Mrs. D. K. N. (W. M. 205075). Duration, eighteen months. Moderately toxic. Eye signs +. Tremor +. Thyroid, slight fullness.

This patient was observed only once and has never been located since.

CASE 52.—Miss C. M. (E. M. 192096, W. S. 194108). Duration, three years. Very toxic. Eye signs + + +. Tremor ++. Thyroid, moderate, soft, symmetrical enlargement. Faint bruit.

She had had two ligations done two years before our observation. She died of acute pericarditis eleven days after lobectomy.

CASE 59.—Miss A. M. B. (W. S. 208734). Duration, eighteen years. Moderately toxic. Eye signs +. Tremor +. Thyroid, slight fullness. Slight bruit.

This patient was observed only once. We have not been able to locate her since.

CASE 62.—Mrs. M. A. H. (O. P. D. 289505, X.Ray 706). Duration, four and one half years. Slightly toxic. Eye signs + +. Tremor + + +. Thyroid, slight symmetrical enlargement.

She had had four roentgen-ray treatments before we started our observations. When seen this year she had had seven more. She was clinically better but her metabolism was unchanged. There still was slight exophthalmos. She had been working for two years.

CASE 68.—Mrs. J. B. (E. M. 213374, X.Ray 524). Duration, seven years. Moderately toxic. Eye signs + +. Tremor +. Thyroid moderate soft, symmetrical enlargement.

She has had prolonged roentgen-ray treatment. Our observations cover the last half of this course only. No change occurred in metabolism, pulse rate or weight during this time, though clinically she appeared to be a little better.

CASE 72.—Miss E. P. (O. P. D. 286790, X.Ray 676). Duration, one month. Slightly toxic. Eye signs +. Tremor +. Thyroid, slight symmetrical enlargement. Faint bruit.

She was observed only twice. This year she writes that she is in good health.

CASE 77.—Mrs. S. I. R. (W. M. and W. S. 210686). Duration, two and one-half years. Very toxic. Eye signs +. Tremor + +. Thyroid, moderate soft symmetrical enlargement. Loud bruit.

She died following a lobectomy.

CASE 89.—Miss M. S. (O. P. D. 300446, X.Ray 817). Duration, eighteen months. Slightly toxic. Eye signs + +. Tremor +. Thyroid, moderate soft symmetrical enlargement. Loud bruit.

She was observed during roentgen-ray treatment, under which she showed no definite improvement. Her present condition could not be learned.

CASE 93.—Mrs. A. B. (W. M. and W. S. 212531, X.Ray 968). Duration, two months. Slightly toxic. Eye signs +. Tremor +. Thyroid, slight soft symmetrical enlargement. Moderate bruit.

She was observed through a course of roentgen-ray treatment which had no apparent effect. She was operated on later, recovered promptly, and has remained well for two years. When seen this year she had no signs or symptoms of exophthalmic goiter. Her metabolism was normal and she was doing housework for a family of four.

CASE 100.—Miss McH. (W. M. 211450). Duration, seventeen months. Slightly toxic. Eye signs +. Tremor +. Thyroid, right lobe palpable. No bruit.

She had had fifteen roentgen-ray treatments before we saw her. She has not been seen this year, but her doctor writes that she has recovered.

CASE 114.—Miss O. S. (O. P. D. 314339, X.Ray 962). Duration, three years. Moderately toxic. Eye signs + + +. Tremor +. Thyroid, marked soft symmetrical enlargement. Bruit present.

She was observed during a course of roentgen-ray treatments. She recovered promptly. When seen this year she presented moderate exophthalmos, but no other signs of exophthalmic goiter. Her metabolism was normal and she was working to full capacity.

CASE 121.—Miss M. M. (E. M. 212253, W. S. 214295, X.Ray 1021). Duration, one year. Very toxic. Eye signs +. Tremor + +. Thyroid, moderate soft symmetrical enlargement. Moderate bruit.

This patient had the highest metabolism of any in the series. She has been studied very completely from the start to the present time. A course of roentgen-ray treatments, together with complete rest, brought her metabolism from + 118 to + 58 per cent., with only a slight fall in pulse rate, and no gain in weight. After lobectomy her metabolism promptly fell to + 15 per cent., with a corresponding fall in pulse. This year she had a metabolism only 11 per cent. above normal and was apparently cured. She received three more roentgen-ray treatments after operation. She had a barely perceptible exophthalmos. She had been working for two years as a domestic.

CASE 130.—Miss K. L. (E. M. 212770). Duration, six weeks. Moderately toxic. Eye signs +. Tremor + + +. Thyroid, moderate soft symmetrical enlargement. Loud bruit.

She showed a definite improvement on rest alone. Later she was operated on in an outside hospital. This year she writes that she is not improved.

CASE 131.—Mrs. S. J. G. (E. M. 229863, X.Ray 1067). Duration, five months. Slightly toxic. Eye signs +. Tremor +. Thyroid, slight fullness. No bruit.

When seen this year, after two years of essentially no treatment, she showed a slight fall in metabolism and pulse rate, gain in weight and slight general improvement.

CASE 138.—Mr. C. J. (O. P. D. 320460). Duration, six years. Moderately toxic. Eye signs + + +. Tremor + +. Thyroid not enlarged.

He was observed for two months only, during which time he took essentially no treatment and showed no change. His present condition could not be learned.

CASE 139.—Mrs. R. K. (O. P. D. 195120, X.Ray 1051). Duration, four years. Slightly toxic. Eye signs + +. Tremor +. Thyroid, moderate soft symmetrical enlargement. Loud bruit.

She was observed twice during roentgen ray treatment. There was no great change in her condition. Her present condition could not be learned.

CASE 144.—Mrs. H. (W. M. 213327). Duration, two years. Slightly toxic. Eye signs +. Tremor +. She had a hemithyroidectomy at the Peter Bent Brigham Hospital in 1914. The remaining lobe of the thyroid was slightly enlarged.

Present condition unknown.

CASE 156.—Theodore D. (W. M. 213713, X.Ray 1060). Duration, five month Moderately toxic. Eye signs + + +. Tremor + +. Thyroid, mode soft symmetrical enlargement. Moderate bruit.

A boy with moderately severe exophthalmic goiter, had four roentgen-ray treatments and this year was much better. All signs and symptoms of thyrotoxicosis were less marked.

CASE 160.—Mr K. (E. M. and W. S. 213989). Duration, two months. Moderately toxic. Eye signs + +. Tremor + +. Thyroid, moderate soft symmetrical enlargement. Moderate bruit.

She got more toxic in spite of complete rest in bed and died after lobectomy.

CASE 161.—Mrs. C. M. (E. M. 213880, W. S. 217740). Duration, eight months. Moderately toxic. Eye signs + +. Tremor +. Thyroid, moderate asymmetrical enlargement. Moderate bruit.

She showed a slight fall in metabolism on rest in bed and died later following a lobectomy.

INTERPRETATION OF DATA

To interpret the data set forth in the preceding tables properly is somewhat difficult. We have sought, by using the basal metabolism as an index of toxicity, to determine the exact effect of roentgen-ray therapy and partial thyroidectomy on the course of exophthalmic goiter. Confusing factors always arise, however. The factor of rest, for instance, or that of drugs, keeps coming in to complicate the picture, as does that of the tendency to spontaneous recovery. Having found that rest alone usually causes the metabolism to fall, we must take great care in attributing observed improvement entirely to surgery or to the roentgen ray. In experimental animals one could study a single factor at a time. This cannot be done with patients if we have proper regard for their welfare. Nevertheless, the present studies bring out a number of interesting points, which we will discuss in turn.

The data of the various cases differs in completeness. It would have been highly desirable if each case had been observed at definitely fixed intervals. This has not been possible. Some patients have been more than willing to come for observation whenever we wished. Others who do not live near Boston have sometimes been able to come only at long intervals. In order to draw conclusions as to the result of treatment, therefore, we have had to separate the cases into groups, each group illustrating some one point.

For purposes of interpretation we have constructed a diagram (Fig. 1). In this are shown, the effect of rest alone, that of rest plus quinin hydrobromid, that of surgery and that of roentgen-ray treatment. The diagram shows average results, represented as columns. To illustrate the effect of rest, for example, we have taken the figures for all cases where observations were secured before and after a period of rest in bed, and averaged the metabolism before and after. The columns represent these averages. The same thing has been done in regard to rest plus quinin hydrobromid. As a matter of fact, these two points are taken directly from Tables 1 and 2 of our first paper.[2]

The data concerning the effect of the roentgen ray has been handled as follows: First, the cases that had been observed before and after roentgen-ray treatment were tabulated, as in Table 3 of our first paper. We then made the following groupings: Group 1, observations secured after from one to two treatments; Group 2, after from three to five treatments; Group 3, after from six to seven

treatments; Group 4, after ten or more treatments, and Group 5, from two to three years after the fifth treatment. These groups were composed for the most part of observations on the same patients, but sometimes, for example, we had observations on a patient to include in Groups 1 and 3, but not in Groups 2 or 4. In a preliminary diagram we arranged five pairs of columns, the first of each pair representing the average metabolism of the group before treatment, the second after treatment. In the diagram actually shown there is but one "before" column which is the average of the five "before"

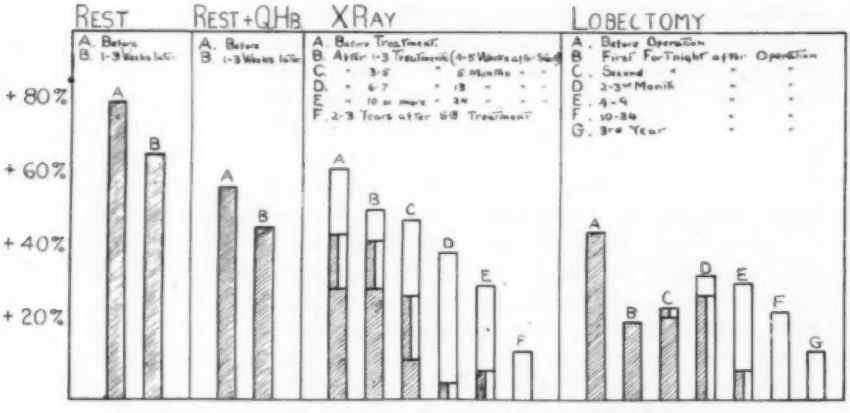


Fig. 1.—Diagram showing average metabolism levels and effect of various sorts of treatment thereon. The columns indicate the percentile increase above the standard. The cases composing each average are enumerated in the Appendix. The method of constructing the diagram is explained in the text. The shading indicates what proportion of the patients forming any average were receiving complete rest (full shading), partial rest (half shading), and what proportion were leading their usual lives (unshaded).

columns of the five groups. The five "after" columns have been reduced to this average "before" column by a simple proportion:

$$B : A = B_2 : A_2$$

in which $B =$ the actual "before" column of the group, B_2 the average "before" column, and $A =$ the actual "after" column of each group, and $A_2 =$ the reduced "after" column shown in the diagram.

This method, while somewhat cumbersome, was rendered necessary by discrepancies in the sequence of observations. However, it finally gives us a satisfactory curve of the effect of the roentgen ray on the largest group of cases available. We did not include in this curve those cases where our first observation was secured only after they had already had roentgen-ray treatment.

The surgical data has been handled in identically the same manner. A statement of exactly what cases were included in the formation of any of the columns in Figure 1 is given in the Appendix.

As we have mentioned before, the factor of rest continually comes in to obscure our deductions. In the diagram, therefore, we have indicated by shading what proportion of the cases were receiving complete or partial rest, and what proportion were leading their usual life.

Effect of Rest.—The first two columns in the diagram show that a group of cases observed at the beginning of a period of complete rest in bed had an average metabolism of + 81 per cent., and that after from one to three weeks the same group had an average of + 67 per cent. A study of the individual metabolism curves of the several cases shows that this drop is a very common, though not inevitable, occurrence. In a few of the more toxic cases, the curve rose in spite of complete rest. It will further be seen on such study that the fall is not progressive. After a time a level is usually reached, and rest alone will not cause a further drop. There is not a single patient in the series whose metabolism was brought to within normal limits by rest alone. These remarks apply to rest in bed over periods of weeks. They do not apply necessarily to rest extending for months or years. We have no observations on the effect of such prolonged rest.

Effect of Quinin Hydrobromid.—We have not studied the action of quinin hydrobromid thoroughly, nor over any long period. Its action when added to that of complete rest over periods of from one to three weeks is shown by the second pair of columns in the diagram. The average metabolism of this group before taking the drug was + 58 per cent. and after taking the drug it was + 47 per cent., a fall no greater than that accomplished by rest alone.

Effect of Roentgen Ray.—The series of roentgen-ray observations are distinctly interesting. The first column, that before treatment was begun, shows an average metabolism of + 63 per cent. At that time a little less than half the patients were getting complete rest, a little less than one-fourth were getting partial rest, and the remainder were following their normal mode of life. The second column, that after one or two treatments, shows a reduction to + 52 per cent. for the group, with relatively rather more of the patients getting complete rest than in the first. After from three to five treatments there is a slight drop, and after six or seven treatments there is a greater drop, with rest playing a lesser and lesser part. Finally, two or three years after the fifth treatment, the group average metabolism is only + 13 per cent. and all the patients are leading normal lives.

Under roentgen-ray treatment, then, the group, as a whole, showed a progressive improvement as measured in terms of the metabolism.

Effect of Surgery.—The group average before lobectomy was + 46 per cent. At that time all the patients were getting complete rest in bed. During the first fortnight after operation there is a very extraordinary fall to + 21 per cent. The next two columns, however, show a secondary rise up to the fourth month after operation. From then on there is a progressive fall, until in the third year the average is + 13 per cent. and all the patients are back leading normal lives. The marked fall in the metabolism immediately after lobectomy, followed by a secondary rise, is very common, though not, as will be seen by studying the individual curves, invariable. It may be due in part to the disturbance caused by the patients leaving the hospital and returning home, but this is not the sole cause, for some increase occurs while they are still in the wards.

Roentgen-Ray Therapy and Surgery Compared.—In the third year, after treatment was well established, the end results in the surgical and roentgen ray groups are identical, namely group averages of + 13 per cent. in each case, with all patients leading normal lives. With the roentgen ray group the improvement was gradual but progressive; with the surgical group there was a sudden marked improvement and a subsequent relapse. The factor of rest was distinctly greater in the surgical group than in the roentgen ray group, yet no more ultimate benefit was, apparently, secured. Moreover, before treatment was begun, the roentgen ray group had a much higher average toxicity than the surgical group, there being an increase in the metabolism of 63 per cent. in the former as against 46 per cent. in the latter. However, since all the surgical cases were resting before operation, while only a part of the roentgen ray cases were resting, the surgical group might be thought to be actually composed of more severe cases than the roentgen ray group. As a mattter of fact, this is not true, however, for the highest metabolism observed in the former group, before the rest period had started, gives an average of only + 61 per cent., which is lower than that of the roentgen ray group before treatment.

It would seem to us, from a study of these results, that the chance of cure in exophthalmic goiter is as good with roentgen-ray treatment as with surgery, in groups of cases of equal toxicity, and that being true, the former method is the preferable, for the danger of fatal outcome is less. Of the nine known deaths occurring in our original series of fifty-five cases, five were directly the result of surgery (Cases 23, 52, 77, 160 and 161). One patient (Case 10) after prolonged roentgen-ray treatment finally died apparently of exoph-

thalmic goiter. Three patients died of unknown causes; one of these (Case 126) after having apparently been cured by operation, one (Case 21) after having apparently been cured by the roentgen ray, and one after failure to improve materially under roentgen-ray therapy (Case 113).

We have given due consideration to the matter of the possible relationship of duration to the improvement in the roentgen ray and surgical groups. It must be admitted that there is a very definite tendency toward spontaneous recovery in exophthalmic goiter. To what extent the improvement in our two groups must be attributed to the natural course of the disease is an unanswerable question. The average duration of the roentgen-ray group in the spring of 1919 was about five and one-half years, while that of the surgical group was about three and one-quarter years. Whether the longer duration in the roentgen-ray group was an important factor in their progress, we cannot say. The lack of relation between duration and end result in individual cases makes it seem unlikely.

Relation of Metabolism to Other Factors.—Up to the present point our discussion has hinged almost entirely on the basal metabolism. The clinical progress, however, has been indicated in the tables. Before closing, it will be well to consider briefly the relation of metabolism to other factors, such as body weight and pulse rate. The respiratory quotients, the blood picture and pathologic findings we intend to study further, and if anything of interest is found it will be reported later.

We have already indicated in our earlier paper[2] that between the basal metabolism and the clinical picture there is a close parallelism. Subsequent observations have for the most part borne this out, although there are occasional exceptions.

To see what, if any, relationship there is between metabolism, weight and pulse, we have plotted these factors in all cases in which five or more observations have been secured. It is not worth while to encumber the present paper with these charts. It may be said, however, that in about 60 per cent. of the cases so charted, there is a close parallelism between pulse and metabolism, and in the remainder a certain amount of parallelism. This is what one would expect, and indicates that in any given case the resting pulse rate is a tolerably good index of the patient's progress. The pulse rate, however, gives comparative results only, for between the metabolism elevation and pulse elevation of different individuals there seems to be but little relationship. The pulse rate, therefore, is not an index of the absolute degree of intoxication in the patient seen for a single time, but it does furnish a relative index in a patient seen at different times.

One would also suppose that the curve of body weight would also bear a definite relationship to the metabolism curve, that when the metabolism fell the weight would increase, that, in other words, the curves would be reciprocal. In about 20 per cent. of the cases there is some evidence of such a reciprocal relationship, but in the rest there is not. Indeed, in some cases we find the exact opposite, the weight increasing with a rising metabolism and vice versa.

The matter of the relationship of metabolism elevation to blood sugar has been discussed by one of us (J. C. A.) in an earlier paper.[23] We have restudied these sugar curves in the light of the present end result data to see whether any information of value in prognosis could be got from the height of the hyperglycemia. No constant relationship of sugar curve to end result could be demonstrated.

Metabolism as a Guide to Treatment.—One may ask, what is to be learned from these studies in regard to the indications for treatment in exophthalmic goiter?

In the first place, as just stated, it seems clear that the majority of patients ultimately do as well with roentgen-ray therapy as with surgery, and that with less hardship to themselves. This being true and in view of the not infrequent fatal outcome of surgical operations on the thyroid, the roentgen-ray form of treatment would seem to be the method of choice. We do not mean by that that surgery is never indicated. Such cases as No. 93 and No. 121 that failed to improve under roentgen-ray therapy and promptly recovered after operation prove that surgery may be necessary. It will, however, be interesting to note in this connection that of a total of twenty-four patients who were operated on, nine had had more or less roentgen-ray treatment before surgery was done. In our diagram the group of columns illustrating the effect of the roentgen ray includes only those patients who received roentgen-ray treatment and rest alone; the group of columns showing the effect of surgery, on the other hand, includes patients who had had roentgen-ray treatment before operation. In this connection we should also like to call attention to the fact that none of the five patients who died following operation had received[24] roentgen-ray treatment beforehand. It is further interesting to note that in the ten postoperative cases in which we have from two to three year end result observations, the basal metabolism of five patients who had roentgen-ray treatments before operation (Cases 71, 88, 93, 121 and 143) averaged + 6 per cent., while that of five patients who were operated on without previous roentgen-ray treatment[24] (Cases 106,

23. Denis, W., and Aub, J. C.: Blood Sugar in Hyperthyroidism, Arch. Int. Med. **20**:964 (Dec.) 1917.

24. This statement is not absolutely true, for a few of these patients had received one roentgen-ray treatment before operation. A single treatment, however, is not of great moment and can be disregarded.

125, 129, 148 and 151) averaged + 20 per cent. The metabolism of the former group of five averaged +44 per cent. before operation and that of the latter + 50 per cent. While the two groups started about evenly, therefore, at the end of two years the group in which surgery was preceded by roentgen-ray treatment showed a far better result than the group in which surgery alone was done.

In view of all this, it seems clear that not only should the roentgen ray be tried first in the management of exophthalmic goiter, with the idea that it may be sufficient to cure the patient, but also because if not alone sufficient to cure, it may render subsequent operation safer, and more likely to be followed by good end results. Surgery, we believe, should be employed with conservatism, and usually only after the roentgen ray and other medical measures have failed. We also believe that after operation, if the metabolism remains elevated, the roentgen ray should again be employed. A case in point is that of (Case 99) Miss M. T. P. with whom no great fall in metabolism was secured by operation but who later definitely improved under roentgen-ray treatment.

In this connection we wish to state that we believe that the roentgen-ray treatment of the thymus is quite as important as that of the thyroid. In the cases that come to operation it seems possible that the safety imparted by previous roentgen-ray treatment is due in some measure to the effect on the former gland.

Numerous writers have felt that the sudden deaths following operations on the thyroid were of thymus origin. Kocher,[25] Halsted[9] and others have performed thymectomies with favorable results. Klose[26] and others have shown that involution of the thymus follows irradiation. Treatment of the thymus by the roentgen ray, therefore, to our minds, should form a part of the pre-operative treatment of exophthalmic goiter. Exposure of the thyroid, we believe, should also be carried out. That roentgen-ray exposures of the thyroid render operations much more difficult through the production of adhesions between gland and capsule, is denied by Dr. C. A. Porter.[27]

Can we now go a step further, and find in these metabolism studies anything that enables us to predict what patients probably will come to operation, and in which ones operation is contraindicated? We believe we can.

A study of the relation of pulse curve to metabolism curve in individual cases shows two fairly definite types: Type 1 in which

25. Kocher, T.: Die Behandlung der Basedowsche Krankh., München. med. Wchnschr. **13**:680, 1910.

26. Klose, H.: Beiträge zur Pathologie und Klinik der Thymusdrüse, Jahrb f. Kinderh. **78**:653, 1913.

27. Porter, C. A.: Personal Communication.

the pulse rate (when plotted in a uniform way with a base line of a pulse rate of fifty and a normal metabolism, and a top line of a pulse rate of 150 and metabolism + 100 per cent.) runs ten or more points above the metabolism curve, and Type 2 in which the pulse curve coincides with, or runs below, the metabolism curve.

Eppinger[28] gives an extreme tachycardia as one of the characteristics of the sympatheticotonic type, while a moderate tachycardia occurs in the vagotonic, and that latter type is presumably that in which there is most pronounced thymus involvement. Without entering into the discussion as to whether two such types actually exist, it occurred to us that it would be well to compare the end results in those of our cases that had an extreme tachycardia and a moderate metabolism elevation on the one hand (Type 1) with those that had an extreme metabolism elevation and a moderate tachycardia (Type 2) on the other hand. For this purpose, belonging to Type 1, we have Cases 66, 71, 88, 93, 110, 135, 143 and 129, and belonging to Type 2, Cases 33, 48, 121, 123, 125, 148 and 151. A study of the end results in these cases shows that the patients of Type 1 did about equally well with surgery or roentgen ray alone, or with surgery preceded by roentgen-ray treatment, while with Type 2 surgery alone gives poor results, the roentgen ray alone may cure, but the roentgen ray followed by surgery may be necessary in the more resistant cases.

Of the five patients who died following operation, four (Cases 23, 52, 160 and 161) belonged to Type 2, and only one (Case 77) belonged to Type 1. The chance of postoperative death, therefore, seems greater in Type 2, at least when roentgen-ray treatment has not been given beforehand.

An apparent contraindication to operation was found in a metabolism rising in spite of the fact that the patient was getting complete rest in bed at the time.

CONCLUSIONS

The conclusions drawn in our first paper are borne out by subsequent work. In addition, we should like to say that using the basal metabolism as an index of toxicity in exophthalmic goiter we have found that:

1. In the majority of cases the results after two or three years are equally good with roentgen-ray treatment as with surgery.

2. That after surgery the metabolism shows a rapid preliminary fall, a secondary rise followed by a final fall, that with roentgen-ray treatment there is a gradual progressive fall.

---

28. Eppinger, H., and Hess, L.: Vagotonie, Sammlung Klinischen Abhandlungsen über Pathologie und Therapie der Stoffwechsel von Noorden, Nos. 9 and 10, Berlin, 1910.

3. That in securing the same end results with surgery or with the roentgen ray, a lesser rest factor is necessary with the roentgen ray. With the roentgen ray there is practically no mortality. With surgery there is a definite one.

4. That patients treated surgically do better, and the risk of operation is less, if they have previously had their thyroid and thymus glands irradiated.

5. That the risk of operation is greater and the need for preoperative roentgen-ray treatment is greater in cases with a very high metabolism and moderate tachycardia than in those with an extreme tachycardia and moderate metabolism elevation.

6. That the safest program for the treatment of exophthalmic goiter, as a whole, is the routine irradiation of thyroid and thymus glands, in all cases, with surgery held in reserve for patients who do not then do well.

7. That surgery is contraindicated with patients whose metabolism is rising in spite of complete rest in bed, and also with patients of the type with moderate tachycardia and great metabolism increase, except when they have previously had thyroid and thymus glands treated by the roentgen ray.

8. Finally, we believe that in the management of exophthalmic goiter, periodic determination of the basal metabolism should be quite as much a routine as is the examination of the urine for sugar in diabetes mellitus. Further, that in borderline cases the basal metabolism furnishes very valuable aid in differential diagnosis.

15 Chestnut Street.

APPENDIX

The columns shown in Figure 1 are made up of observations on various cases as follows:

Rest Series: Cases 10, 88, 111, 121, 137, 151.

Quinin Hydrobromid Series: Cases 3, 77, 99, 117, 126, 130, 131, 135, 160, 161.

Roentgen-Ray Series:

From one to two treatments.—Cases 10, 21, 48, 93, 110, 111, 113, 120, 121, 123, 131, 135.

From three to five treatments.—Cases 21, 25, 33, 53, 66, 93, 107, 110, 111, 113, 120, 121, 123, 156.

From six to seven treatments.—Cases 12, 25, 33, 48, 53, 66, 110, 123, 135.

Ten or more treatments.—Cases 10, 48, 66, 111.

From two to three years after the fifth treatment.—Cases 33, 48, 66, 110, 111, 123, 135.

Surgical Series:

First fortnight.—Cases 71, 83, 88, 93, 117, 121, 125, 126, 137, 143.

Second fortnight.—Cases 3, 88, 93, 99, 106, 117, 125, 126, 143, 151.

Second and third months.—Cases 71, 83, 88, 93, 99, 106, 117, 125, 126, 130, 137, 143.

From fourth through ninth month.—Cases 71, 88, 99, 106.

From tenth through twenty-fourth month.—Cases 3, 16, 88, 93, 126.

Third year.—Cases 71, 88, 93, 106, 121, 125, 129, 143, 148, 151.

THE MORE COMMON GASES; THEIR EFFECT ON THE RESPIRATORY TRACT

OBSERVATION ON TWO THOUSAND CASES

ROBERT S. BERGHOFF, M.D.
CHICAGO

Recent medical literature, both domestic and foreign, relative to the effect on the respiratory system of the various gases employed as part and parcel of the chemical warfare in the war has been rather meager. Especially is there a scarcity of information regarding a study of gas cases in their chronic stage. With the aid of a bibliography from the surgeon-general's library, we have combed over carefully foreign and domestic relative matter, and were able to find comparatively little. It is with a degree of temerity and hesitancy, therefore, that this (pioneer) work is undertaken. I experience a certain amount of moral courage, however, in confining myself solely to observations and clinical findings, and in avoiding conclusions. The clinical data embodied in this paper are based on the observation of about two thousand cases studied in the capacity of review examiner on the medical examining board at Camp Grant, Ill.

Under the present war department regulations, all gassed soldiers coming up for discharge, irrespective of the presence or absence of symptoms or findings, are referred by the general heart and lung examiners to the board of review for disposition. In an atmosphere of quiet, these men are examined thoroughly and the degree of disability, and the amount of compensation determined. Since Dec. 1, 1918, approximately two thousand such cases have been referred to the review board at Camp Grant, and of them this paper will attempt a classification, comparative study, and a few original observations and deductions.

In determining the type of gas to which the individual soldier was subjected, we have been obliged to place a great deal of dependence on the personal history. The overseas records in many instances merely attested to the fact that the soldier had been gassed, and gave the length of his stay in the hospital. However, we have found the matter of history very reliable. The average soldier evidences a lively interest in himself and in his condition, and is able not only to name the type of gas with which he was affected, but gives a connected intelligible description of his early and late symptoms. So that the element of conjecture and uncertainty is quite negligible, and after careful ques-

tioning, we feel reasonably certain of the correctness and authenticity of our classification.

As is quite generally known, gassing occurred in one of two distinctly different ways. The first, which was most common in the early days of the war, was through the medium of a gas attack — the laying down of a barrage followed by a "gas cloud." This gas cloud or "drift gas," as it was originally known, consisted of chlorin, or chlorin plus a synthetic compound. As the war progressed, drift attacks for diverse reasons were modified and to a more or less degree replaced by high explosive gas shells. In our observation of two thousand cases, we encountered 240 men who sustained their gas poisoning through cloud or drift gassing, the remainder through high explosives. The gasses of the high explosive shells were of several varieties. We have prepared a table for the comparative study of these gasses and have divided the table into two distinct groups. Group 1 includes those men who sustained their poisoning through cloud or drift attacks, the type of gas being chlorin; Group 2 includes the remainder, all those subjected to high explosive gassing. This latter group includes mustard gas as the most important numerically, chlorin as equally important because of its severity and toxicity, phosgene, chloropicrin and a mixed gas. Our table offers not only a list of gases encountered with the number of cases in each list, but offers also a comparative study of the severity of each type, the symptoms complained of, the length of hospitalization of the individuals. The more important gases will be gone into in detail, chlorin being given the greatest attention, because of its frequency and severity. Just a word at this time about the information gathered through a comparative study of the effects of chlorin gas in Groups 1 and 2. The table shows unmistakably that cases of chlorin gas poisoning in Group 1, the men subjected to cloud attacks, were more severe, called for longer hospitalization, showed more extensive physical findings, and threatened a more protracted convalescence than did the chlorin cases of Group 2, the men subjected to chlorin through high explosive shells.

Chlorin.—We have singled out chlorin for a more detailed study and discussion for several reasons. In the first place, except for mustard gas, which represented more than 30 per cent. of all our cases, chlorin was the most common type encountered. Mustard gas, while it affected the lungs very markedly, and in many cases produced interesting respiratory physical findings, must, nevertheless, be considered a surface gas rather than a pure inhalatory type gas. In the second place, chlorin gas cases presented a history and subjective symptoms of greater severity and longer duration and longer hospitalization, and physical examination of the men, on an average of four months after

the attack, showed more real palpable findings than did any other type of gas poisoning encountered.

The average gas case appearing before the review board at Camp Grant was in the chronic stage of disease, having sustained the attack on an average of from three or four months prior to the final examination, consequently we are forced to depend for a description of the acute stage on the recent medical literature covering that phase of the subject. Monographs covering the early course of gas cases are both prolific and thorough. We have selected one entitled, "Lecture on Gas Poisoning," by Hill,[1] and will quote freely from his paragraphs on symptoms and pathology.

Under symptomatology, Hill says: "The typical case is cold, with a subnormal temperature, pulse is slow and full. The face is cyanosed and the posture is one gasping for breath. The respirations are jerky, often numbering forty a minute, associated with a choking cough and a frothy expectoration. With each inspiration the chest is expanded to its fullest, all the auxiliary muscles being brought into play. This first is the asphyxial stage which usually lasts about thirty-six hours. This stage is followed by symptoms of bronchitis. There is a greenish mucopurulent expectoration, high temperature, small rapid pulse (160), and the respirations are shallow and fast (60). Diminished expansion is one of the most pronounced physical findings at this time, and is due, we thought, to the contraction of the bronchial tubes."

Speaking of prognosis, Hill says: "There seems no reason why recovery of the lungs should be any less perfect after chlorin poisoning than it is after bronchopneumonia." Hill concludes his paragraph on prognosis with these words: "I have no evidence to offer as to the state of the lungs at any long period after the poisoning." That experience we have had in abundance at Camp Grant. Our work began where Hill left off. Hill saw the patient in the acute stage, we saw him in the chronic stage. Hill studied the subject from one to four days after the attack, we had him under observation from three to four months later. Our findings and conclusions are recorded elsewhere in this paper. We agree with Hill in his statement on prognosis. We, too, feel that there is no apparent reason why these subjects should not regain normal respiratory function and rid themselves of their gradually disappearing symptoms.

For the pathology on gas poisoning, we are also dependent on the literature. While the mortality in acute cases was high, and consequent necropsies were numerous, conversely the mortality in the chronic cases is negligible and necropsies sparse. The morbid anatomy records

1. Hill, L.: J. Roy. Army Med. Corps, London **26**: (Jan.) 1916.

of the acute cases are in keeping with the physical findings. Hill describes his postmortem findings as follows: "The mucosa of the trachea and larger bronchi shows intense congestion. The lungs do not collapse in these acute cases, but appear like a solid cast of the thoracic cavity, and are greatly increased in weight. On incision, the lung tissues appear of a deep maroon red color, and the exudation flows from the cut surface in abundance. Light gray patches are to be seen on the surface of the lung amidst the congested areas. They were found to be due to emphysema. So intense is the obstruction to the entry of air, and so violent the efforts of respirations, that emphysema is produced in these least poisoned parts where air can still enter. The parts of the lung not affected by emphysema show intense congestion of the capillaries, and many of the alveoli are seen filled with exudate. Death is probably brought about by stasis in the pulmonary vessels."

GROUP 1. GAS SUSTAINED IN CLOUD OR DRIFT ATTACK

No.	Chlorin	Mustard	Phosgene	Chloropierin	Mixed	Time in Hospital	Cough	Findings
240	240	...	...	...	...	4 months	60%	8%

GROUP 2. GAS SUSTAINED THROUGH HIGH EXPLOSIVE GAS SHELLS

	280	280	...	...	...	...	3 months	23%	3%
	741	...	741	...	...	...	11 weeks	20%	6%
	186	...	...	186	...	...	9 weeks	28%	3.5%
	33	...	...	...	33	...	5 weeks	17%	1.5%
	515	...	...	...	...	515	10 weeks	22%	8%
Total	2,000								

It will be seen that the necropsy findings just enumerated coincide in detail with the physical findings elicited even after four months of the disease (which are considered in a later paragraph). We have been able to map out distinctly patches or areas of diminished breath sounds and an accompanying tympanitic percussion note which undoubtedly correspond with an underlying area of stretched and dilated alveoli—an emphysema. Before leaving the subject of morbid anatomy in chlorin gas cases, we wish to quote the report on a postmortem examination of a German prisoner of war who died from the effects of chlorin poisoning. The case is reported by Crabbe,[2] and emphasizes what has already been said: "Postmortem: The patient was gassed September 25, presumably by chlorin or some chlorin compound. When admitted to the Base Hospital he was slightly cyanosed and had a yellowish toxic appearance. The respirations were on the average 60, and the pulse rate 120. There was some rise of

2. Crabbe: J. Roy. Army Med. Corps, London **26**: (Jan.) 1916.

temperature. The symptoms were more toxic than bronchitic, the cough was not severe. He died October 4, at 8 a. m.

"Postmortem: Pleura adherent both sides and base; adhesions easily broken down; no fluid in the pleura. Lungs appeared to be distended with marked emphysema. On section they showed marked emphysema and particularly toward the apices; the bases were congested. There was a general purulent bronchitis with marked increase of pus towards the apices. The bases were cyanosed. The contained blood was almost black, but the coagulability was below normal. Both lungs floated, also sections from apex and base.

"Trachea: The mucous membrane was coated with mucopus and infected, the infection increasing toward the bifurcation. There were old glands at the bifurcation."

Here, again, we not only have the necropsy findings of emphysema and bronchitis to correspond with similar physical findings, but we find a complete agreement in detail. The patches of emphysema detected in physical examination are shown in the necropsy room, and the preponderance of bronchial râles at the bases and over the large bronchial trunks, are shown to emanate from the moisture collected there. In chronic gas poisoning, therefore, and more specifically in chronic chlorin gas poisoning, as evidenced by physical findings, corroborated by necropsy, we are dealing with a pathology of one of two distinct varieties: (1) Bronchitic; (2) emphysematous, or (3) a combination of the two.

A comparative study of the history and early symptoms of the three most frequent and most important gases, mustard, chlorin and phosgene, reveals some interesting differences.

Mustard Gas.—Perhaps the most frequent and most pronounced early symptom of mustard gas poisoning complained of by the soldier is that of hemorrhage and bleeding from the nose. We are astonished at the frequency with which that symptom was given as the most annoying of the early results of mustard gassing. Cough, shortness of breath, sneezing and other signs of irritability of the air passages were included in the anamnesis, but hemorrhage held first place. With many it seems to have been very mild, in some instances merely a frothy blood tinged sputum or inconsequential epistaxis; in others, a true hemorrhage of such magnitude, that it must have caused concern to the individual as well as the army surgeon in charge.

Chlorin Gas.—Almost as prominent as the history of hemorrhage in mustard gas, is the complaint of a suffocation, a distressing inability to get enough air, in chlorin gas poisoning. These patients complained of cough, a few of hemorrhage, but the important universal early symptom experienced was in effect a sense of constriction around the

chest, a tightness in the throat, and a panting for breath. This condition lasted from twenty-four to seventy-two hours, and gave way to a chronic cough, with general irritability of the air passages.

Phosgene Gas. — Patients suffering from phosgene gassing complained of cough, bloody sputum, sneezing, but mainly of weakness — a general weakness which came on as early as two hours after gassing, and as late as three days, and lasted for weeks and even months. Long after the cough had disappeared, this weakness remained.

Physical Findings.—The physical findings of any or all of our two thousand gas cases at an average period of four months after the attack will admit of a fairly nice classification into three groups:

1. Normal Group: The apparently normal group, as the table will show, includes almost 50 per cent. of the total. A careful thorough physical examination fails to reveal any abnormalities. Expansion is normal, the breath sounds are clear and vesicular. The percussion note is negative and there is no moisture. And in the face of these apparently normal physical findings, there is oftentimes a complaint of cough, shortness of breath on exertion, all of which presents a disconcerting problem. With the complaint of respiratory distress and without definite physical findings, and no apparent pathology, we have no guide toward a logical prognosis.

2. Bronchitic Group: This group includes practically 30 per cent. of all cases examined. The findings are rather definite, and do not differ materially from the subacute and chronic bronchitis ordinarily encountered. The type of breathing is harsh and high-pitched throughout. Expiration is prolonged and at times interrupted, most pronounced after exercise. Moisture is abundant. There are coarse, moist râles rather evenly distributed, most pronounced over the bronchial trunks and at the bases, occasionally fine, moist râles in the apices which disappear on coughing. When we remember that these findings are in evidence as long as five months after the acute onset, we are impressed with the toxicity of the initial irritant action on the mucous membranes of the respiratory tract, and we are apt to conjecture on the probable duration of the findings and the ultimate result.

3. Emphysema Group: The third group, which included about 22 per cent. of our two thousand cases, was characterized by the presence of an emphysema. On inspection, the chest seemed moderately rigid, the movements of the diaphragm limited, expansion impaired, and the accessory muscles in use. On palpation tactile fremitus was markedly diminished, and in some instances entirely absent. On percussion, a hyper-resonant note was detected. On auscultation the breath sounds over the entire chest, except the bronchial area, were

much diminished and faint. In some cases we were able to map out discrete patches of emphysema.

In confirmation of the physical findings just enumerated, we found in a paper by Elliott[3] the following: "On physical examination one notes a marked limitation of movement of the apices of the lungs. The chest seems fixed as in an old emphysema. The respiratory murmur is usually faint above and below the clavicular area, though at times harsh in the infraclavicular. The adventitious sounds are variable, but when present are those of a bronchitis or bronchiolitis.

Prognosis.—In considering the prognosis of a disease or condition in which marked subjective symptoms are contrasted with meager or entirely absent physical findings, we are seriously handicapped, and our conclusions must be more or less conjecture. This is especially so if we are denied the help of past experience. In our review of two thousand gas cases we are confronted with just this difficulty. Nevertheless, we have after careful individual and group examination and comparison, arrived at rather definite conclusions:

1. That gas victims, irrespective of the type of gas and severity of attack sustained, show no marked predisposition toward active pulmonary tuberculosis, or toward the reactivation of a healed or quiescent pulmonary lesion.

2. That gas victims present little evidence of material destruction of lung tissue.

3. That gas victims with emphysema findings have a more protracted convalescence than have those of the bronchitic group.

---

3. Elliott, J. H.: Internat. J. S. (Dec.) 1918.

INDEX TO VOLUME 24

PAGE

Acid, acetylsalicylic, and heat regulation in fever cases; Henry G. Barbour 624

Acid, acetylsalicylic, and heat regulation in normal individuals; Henry G. Barbour and Michael M. Devenis 617

Acidosis, control of, in treatment of diabetes; Edgar Stillman 445

Allen, Frederick M.: Three cases of "renal glycosuria" 523

Amebiasis, criterions for distinguishing endamoeba of, from other organisms; Charles A. Kofoid, Sidney I. Kornhauser and Olive Swezy 35

Antipyretics. I. The Benedict respiration chamber at the New Haven Hospital; Henry G. Barbour 611

Antipyretics. II. Acetylsalicylic acid and heat regulation in normal individuals; Henry G. Barbour and Michael M. Devenis 617

Antipyretics. III. Acetylsalicylic acid and heat regulation in fever cases; Henry G. Barbour 624

Asthenia, neurocirculatory: See Heart, irritable

Asuzano, M. A.: Two cases of endamebic dysentery at Baguio hospital treated with benzyl benzoate 396

Aub, J. C.: Basal metabolism in exophthalmic goiter 645

Aub, J. C.: Basal metabolism in hypothyroidism 404

Auscultatory phenomena of heart in normal men and in soldiers with irritable heart; John T. King, Jr 89

Balcar, J. O.: Fever and water reserve of body 116

Barach, Joseph H.: Energy index (S. D. R. index) of circulatory system 509

Barbour, Henry G.: Antipyretics. I. Benedict respiration chamber at New Haven Hospital 611

Barbour, Henry G.: Antipyretics. II. Acetylsalicylic acid and heat regulation in normal individuals 617

Barbour, Henry G.: Antipyretics. III. Acetylsalicylic acid and heat regulation in fever cases 624

Barron, Moses: Necropsy studies at a hospital center 302

Baumann, L.: Uric acid content of blood compared with renal dietary test 70

Beaven, Paul Webley: Clinical evidence of involvement of suprarenal glands in influenza and influenzal pneumonia 78

Benedict respiration chamber at the New Haven Hospital; Henry G. Barbour 611

Benzyl benzoate in treatment of endamebic dysentery at Baguio hospital; M. A. Asuzano 396

Benzyl benzoate, protozoologic and clinical studies on treatment of protozoal dysentery with; Frank G. Haughwout and Pedro T. Lantin ... 383

PAGE

Berghoff, Robert S.: The more common gases; their effect on respiratory tract 678

Berman, Louis: Determination of hemoglobin by the acid hematin method 553

Blood, cholesterol content of, in various hepatic conditions; M. A. Rothschild and J. Felsen..... 520

Blood, uric acid content of, compared with renal dietary test; bland diet compared with ordinary test diet; L. Baumann, G. H. Hansmann, A. C. Davis and F. A. Stevens..... 70

Boas, Ernst P.: Relation of neurocirculatory asthenia to hyperthyroidism as determined by effects of injection of epinephrin..... 419

Boettiger, Carl: Pneumonia and some of its complications at Camp Bowie 1

Botulism. Study of the resistance of spores of bacillus botulinus to various sterilizing agencies employed in canning fruits and vegetables; Ernest C. Dickson, Georgina S. Burke and Engelena S. Ward..... 581

Bridgman, E. W.: Duration of normal convalescence..... 65

Brown, N. Worth: Sino-atrial heart block in child, with observations on effects of atropin and vagus stimulation..... 458
(Correction) 580

Burke, Georgina S.: Botulism. Study of the resistance of spores of bacillus botulinus to various sterilizing agencies employed in canning fruits and vegetables 581

Canning, study of resistance of spores of bacillus botulinus to various sterilizing agencies employed in canning fruits and vegetables; Ernest C. Dickson, Georgina S. Burke and Engelena S. Ward..... 581

Carter, Edward Perkins: The electrocardiogram and ventricular preponderance 638

Charlton, Alice G.: Experimental endothelial leukocytosis in guinea-pigs, fifth report of studies on mononuclear leukocytes of blood..... 295

Cholesterol content of blood in various hepatic conditions; M. A. Rothschild and J. Felsen..... 520

Clough, Harry D.: Studies on epinephrin. III. Effect of epinephrin on electrocardiograms of patients with "irritable heart"..... 284

Colwell, Howard S.: Pneumonia and some of its complications at Camp Bowie 1

Contagious diseases, immunity of city-bred recruits; A. G. Love and Charles B. Davenport..... 129

Convalescence, normal, duration of; E. W. Bridgman..... 65

Cowie, David Murray: Clinical evidence of involvement of suprarenal glands in influenza and influenzal pneumonia..... 78

Davenport, Charles B.: Immunity of city-bred recruits..... 129

Davis, A. C.: Uric acid content of blood compared with renal dietary test 70

Devenis, Michael M.: Antipyretics. II. Acetylsalicylic acid and heat regulation in normal individuals..... 617

Diabetes, control of acidosis in treatment of; Edgar Stillman..... 445

PAGE

Dickson, Ernest C.: Botulism. Study of the resistance of spores of bacillus botulinus to various sterilizing agencies employed in canning fruits and vegetables 581

Dysentery, endamebic, at Baguio hospital treated with benzyl benzoate; M. A. Asuzano 396

Dysentery, protozoologic and clinical studies on treatment of protozoal dysentery with benzyl benzoate; Frank G. Haughwout and Pedro T. Lantin 383

Effort Syndrome: See Heart, Irritable.

Electrocardiogram and ventricular preponderance; Edward Perkins Carter and Carl H. Greene..... 638

Electrocardiogram, significance of abnormalities in form of; G. Canby Robinson 422

Electrocardiograms, effect of epinephrin on, of patients with "irritable heart;" Harry D. Clough..... 284

Emphysema, experimental; Sarah R. Kelman..... 332

Endamoeba, criterions for distinguishing endamoeba of amebiasis from other organisms; Charles A. Kofoid, Sidney I. Kornhauser and Olive Swezy 35

Energy index (S. D. R. index) of circulatory system; Joseph H. Barach.. 509

Epinephrin, relation of neurocirculatory asthenia to hyperthyroidism as determined by injection of epinephrin; Ernst P. Boas..... 419

Epinephrin, studies on. I. Effects of injection of epinephrin in soldiers with "irritable heart;" Joseph T. Wearn and Cyrus C. Sturgis..... 247

Epinephrin, studies on. II. Effects of epinephrin on basal metabolism in soldiers with "irritable heart," in hyperthyroidism and in normal men; Edna H. Tompkins, Cyrus C. Sturgis and Joseph T. Wearn..... 269

Epinephrin, studies on. III. Effect of epinephrin on electrocardiograms of patients with "irritable heart;" Harry D. Clough..... 284

Felsen, J.: Cholesterol content of blood in various hepatic conditions.... 520

Fever and water reserve of body; J. O. Balcar, W. D. Sansum and R. T. Woodyatt 116

Foster, Nellis B.: Increase of extract nitrogen in tissues, with chronic nephritis 242

Gases, more common; their effect on the respiratory tract; Robert S. Berghoff 678

Glycosuria, renal, three cases of; Frederick M. Allen, Mary B. Wishart and L. Millard Smith..... 523

Goiter, exophthalmic, and basal metabolism; J. H. Means and J. C. Aub.. 645

Gordon, Alfred: Mental disorders following influenza..... 633

Gout, roentgenographic studies in gout; C. W. McClure and E. D. McCarty 563

Greene, Carl H.: The electrocardiogram and ventricular preponderance.. 638

Greenway, James C.: Pneumonia and some of its complications at Camp Bowie 1

PAGE

Haden, Russell L.: Meningococcus meningitis at Camp Lee..... 514

Hall, Milton W.: Study of pneumococcus carriers..... 600

Hansmann, G. H.: Uric acid content of blood compared with renal dietary test 70

Haughwout, Frank G.: Protozoologic and clinical studies on treatment of protozoal dysentery with benzyl benzoate..... 383

Heart, auscultatory phenomena of, in normal men and in soldiers with irritable heart; John T. King, Jr..... 89

Heart block, sino-atrial in child, with observations on effects of atropin and vagus stimulation; N. Worth Brown..... 458

(Correction) 580

Heart, irritable, effect of epinephrin on electrocardiograms of patients with; Harry D. Clough..... 284

Heart, irritable, effects of injection of epinephrin in soldiers with; Joseph T. Wearn and Cyrus C. Sturgis..... 247

Heart, irritable, effects of epinephrin on basal metabolism in soldiers with "irritable heart," in hyperthyroidism and in normal men; Edna H. Tompkins, Cyrus C. Sturgis and Joseph T. Wearn..... 269

Heart, irritable, in general practice; comparison between it and irritable heart of soldiers; S. Neuhof..... 51

Heart, irritable, possibilities of physical development in cases of effort syndrome by means of graded exercises; Bertnard Smith..... 321

Heart, irritable, relation of neurocirculatory asthenia to hyperthyroidism as determined by effects of injection of epinephrin; Ernst P. Boas.... 419

Heart, irritable, study of incidence of pulmonary tuberculosis in soldiers with; John T. King, Jr..... 238

Heart, prolongation of the "S-T" interval of the ventricular complex as shown by the electrocardiograph; Jonathan Meakins..... 489

Heart sounds, factors determining relative intensity of, in different auscultation areas; Carl J. Wiggers..... 471

Hemoglobin, determination of, by the acid hematin method; Louis Berman 533

Higley, Henry Allen: Study of renal concentration power for uric acid in early chronic interstitial nephritis..... 557

Howard, C. P.: Progressive lenticular degeneration associated with cirrhosis of liver (Wilson's disease)..... 497

Hyperthyroidism, effects of epinephrin on basal metabolism in soldiers with "irritable heart," in hyperthyroidism and in normal men; Edna H. Tompkins, Cyrus C. Sturgis and Joseph T. Wearn..... 269

Hyperthyroidism, relation of neurocirculatory asthenia to, as determined by effects of injection of epinephrin; Ernst P. Boas..... 419

Hyperthyroidism, use of laboratory methods in diagnosis of; Charles W. Lueders 432

Hypothyroidism, basal metabolism in; J. H. Means and J. C. Aub..... 404

Immunity of city-bred recruits; A. G. Love and Charles B. Davenport..... 129

PAGE

Influenza and neurosyphilis; Karl A. Menninger..... 98

Influenza, clinical evidence of involvement of suprarenal glands in influenzal pneumonia and; David Murray Cowie and Paul Webley Beaven..... 78

Influenza epidemic of autumn, 1918, pathologic anatomy and bacteriology of; Baldwin Lucke, Toynbee Wight and Edwin Kime..... 154

Influenza, mental disorders following; Alfred Gordon..... 633

Kelman, Sarah R.: Experimental emphysema..... 332

Kerr, William J.: Preliminary survey of thyroid gland among 2,182 recruits at Camp Lewis, Washington..... 347

Kime, Edwin: Pathologic anatomy and bacteriology of influenza..... 154

King, John T., Jr.: Auscultatory phenomena of heart in normal men and in soldiers with irritable heart..... 89

King, John T., Jr.: Study of incidence of pulmonary tuberculosis in soldiers with irritable heart..... 238

Kofoid, Charles A.: Criterions for distinguishing endamoeba of amebiasis from other organisms..... 35

Kornhauser, Sidney I.: Criterions for distinguishing endamoeba of amebiasis from other organisms..... 35

Lantin, Pedro T.: Protozoologic and clinical studies on treatment of protozoal dysentery with benzyl benzoate..... 383

Lenticular degeneration, progressive, associated with cirrhosis of liver; C. P. Howard and C. E. Royce..... 497

Leukocytosis, experimental endothelial, in guinea-pigs; fifth report of studies on mononuclear leukocytes of blood; Frank A. McJunkin and Alice G. Charlton..... 295

Liver, cholesterol content of blood in various hepatic conditions; M. A. Rothschild and J. Felsen..... 520

Liver, cirrhosis of, with progressive lenticular degeneration (Wilson's disease); C. P. Howard and C. E. Royce..... 497

Love, A. G.: Immunity of city-bred recruits..... 129

Lucke, Baldwin: Pathologic anatomy and bacteriology of influenza..... 154

Lueders, Charles W.: Use of laboratory methods in diagnosis of early hyperthyroidism..... 432

McCarty, E. D.: Roentgenographic studies in gout..... 563

McClure, C. W.: Roentgenographic studies in gout..... 563

McCoy, Charles: Study of pneumococcus carriers..... 600

McJunkin, Frank A.: Experimental endothelial leukocytosis in guinea-pigs; fifth report of studies on mononuclear leukocytes of blood..... 295

Meakins, Jonathan: Prolongation of the "S-T" interval of the ventricular complex as shown by electrocardiograph..... 489

Means, J. H.: Basal metabolism in exophthalmic goiter..... 645

Means, J. H.: Basal metabolism in hypothyroidism..... 404

Meningitis, meningococcus, at Camp Lee; Russell L. Haden..... 514

PAGE

Menninger, Karl A.: Influenza and neurosyphilis 98

Mental disorders following influenza; Alfred Gordon 633

Metabolism, basal, effects of epinephrin on, in soldiers with "irritable heart," in hyperthyroidism and in normal men; Edna H. Tompkins, Cyrus C. Sturgis and Joseph T. Wearn 269

Metabolism, basal, in exophthalmic goiter; J. H. Means and J. C. Aub 645

Metabolism, basal, in hypothyroidism; J. H. Means and J. C. Aub 404

Necropsy studies at a hospital center; Moses Barron 302

Nephritis, chronic, increase of extract nitrogen in tissues with; Nellis B. Foster 242

Nephritis, interstitial, early, chronic, study of renal concentration power for uric acid in; Roy Upham and Henry Allen Higley 557

Nephritis, production of Bright's disease by feeding high protein diets; L. H. Newburgh 359

Nervous system, syphilis of, and influenza; Karl A. Menninger 98

Neuhof, S.: Irritable heart in general practice; comparison between it and irritable heart of soldiers 51

Neurosyphilis: See Nervous System, Syphilis of.

Newburgh, L. H.: Production of Bright's disease by feeding high protein diets 359

Nitrogen, increase of extract nitrogen in tissues, with chronic nephritis; Nellis B. Foster 242

O'Malley, John J.: Cutaneous reaction and desensitization in quinin idiosyncrasy 378

Pearl, Raymond: Statistical discussion of relative efficacy of different methods of treating pneumonia 398

Pneumococcus carriers; Joseph Sailer, Milton W. Hall, Robert L. Wilson and Charles McCoy 600

Pneumonia and some of its complications at Camp Bowie; James C. Greenway, Carl Boettiger and Howard S. Colwell 1

Pneumonia, group of 68 cases of Type I pneumonia occurring in 30 days at Camp Upton with special reference to serum treatment; Charles F. Tenney and William T. Rivenburgh 545

Pneumonia, influenzal, clinical evidence of involvement of suprarenal glands in influenza and influenzal pneumonia; David Murray Cowie and Paul Webley Beaven 78

Pneumonia, statistical discussion of relative efficacy of different methods of treating pneumonia; Raymond Pearl 398

Quinin idiosyncrasy, cutaneous reaction and desensitization in; John H. O'Malley and DeWayne G. Richey 378

Recruits, city-bred, immunity of; A. G. Love and Charles B. Davenport ... 129

Richey, DeWayne G.: Cutaneous reaction and desensitization in quinin idiosyncrasy 378

Rivenburgh, William T.: Groups of 68 cases of Type I pneumonia occurring in 30 days at Camp Upton 545

PAGE

Robinson, G. Canby: Significance of abnormalities in form of electrocardiogram 422

Rothschild, M. A.: Cholesterol content of blood in various hepatic conditions 520

Royce, C. E.: Progressive lenticular degeneration associated with cirrhosis of the liver (Wilson's disease) 497

Sailer, Joseph: Study of pneumococcus carriers 600

Sansum, W. D.: Fever and water reserve of body 116

Smith, Bertnard: Possibilities of physical development in cases of effort syndrome by means of graded exercises 321

Smith, L. Millard: Three cases of "renal glycosuria" 523

Stevens, F. A.: Uric acid content of blood compared with renal dietary test 670

Stillman, Edgar: Control of acidosis in treatment of diabetes 445

Sturgis, Cyrus C.: Studies on epinephrin. I. Effects of injection of epinephrin in soldiers with "irritable heart" 247

Sturgis, Cyrus C.: Studies on epinephrin. II. Effects of epinephrin on basal metabolism in soldiers with "irritable heart," in hyperthyroidism and in normal men 369

Suprarenal glands, clinical evidence of involvement of, in influenza and influenzal pneumonia; David Murray Cowie 78

Swezy, Olive: Criterions for distinguishing endamoeba of amebiasis from other organisms 35

Tenney, Charles F.: Group of 68 cases of Type I pneumonia occurring in 30 days at Camp Upton 545

Thyroid gland, preliminary survey of, among 2,182 recruits at Camp Lewis, Washington; William J. Kerr 347

Tompkins, Edna H.: Studies on epinephrin. II. Effects of epinephrin on basal metabolism in soldiers with "irritable heart," in hyperthyroidism and in normal men 269

Tuberculosis, pulmonary, study of incidence of, in soldiers with irritable heart; John T. King, Jr 238

Upham, Roy: Study of renal concentration power for uric acid in early chronic interstitial nephritis 557

Uric acid content of blood compared with renal dietary test; L. Baumann, G. H. Hansmann, A. C. Davis and F. A. Stevens 70

Uric acid, study of renal concentration power for, in early chronic interstitial nephritis; Roy Upham and Henry Allen Higley 557

Ward, Engelena S.: Botulism. Study of the resistance of spores of bacillus botulinus to various sterilizing agencies employed in canning fruits and vegetables 581

Water reserve of body and fever; J. O. Balcar, W. D. Sansum and R. T. Woodyatt 116

Wearn, Joseph T.: Studies on epinephrin. I. Effects of injection of epinephrin in soldiers with "irritable heart" 247

PAGE

Wearn, Joseph T.: Studies on epinephrin. II. Effects of epinephrin on basal metabolism in soldiers with "irritable heart," in hyperthyroidism and in normal men..... 269

Wiggers, Carl J.: Factors determining relative intensity of heart sounds in different auscultation areas..... 471

Wight, Toynbee: Pathologic anatomy and bacteriology of influenza..... 154

Wilson, Robert L.: Study of pneumococcus carriers..... 600

Wilson's disease; C. P. Howard and C. E. Royce..... 497

Wishart, M. B.: Three cases of "renal glycosuria"..... 523

Woodyatt, R. T.: Fever and water reserve of body..... 166

The American Medical Association will pay 50 cents each for the following issues of the Archives of Internal Medicine: January, March, June and August, 1918. January and July, 1916; November, 1915; January, 1911; July, 1909. Address to AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.

A WORLD GRASP ON MEDICAL LITERATURE

To read all of the worthwhile medical literature of the day is out of the question. To keep one in close touch with the medical thought of the world; to enable one quickly to select just what is related to his special interests; to simplify, systematize and clarify all worthwhile current medical contributions is a service which most reading physicians will at once appreciate. This service is supplied through the

Quarterly Cumulative Index to Current Medical Literature

It enables the user in a minute's time to locate the recent worthwhile contributions to any medical subject. It tells what has been written on that subject; who wrote it; when it appeared; in what publication, and where the publication may be obtained.

It saves time, saves labor and enables even the busiest man to keep tab on the contributions relating to his special problems or interests. To illustrate: A recent issue lists 114 articles under "Heart." These cover fifty-four phases of the subject; they are compiled from forty-seven different journals, and represent fourteen different countries of the world.

Special Features of the Index

Authors and Titles in One Alphabet Oftimes the inquirer knows the name of the author and the subject matter of his article but not the exact title. Sometimes the reverse is true. With the Quarterly Cumulative Index either the name or title is sufficient to locate the article as both are included in the same alphabetical arrangement.

Issued Four Times a Year April, July, October and January. Each new number includes all references in the earlier numbers of the current year; at no time during the year is it necessary to consult more than one alphabet. The fourth or last number for the year is bound in cloth for permanent reference.

A Reliable Index In its preparation the original articles are consulted and reviewed so that the reference will really "refer" not only to the title but also to the subject matter of the article. Every effort is made and no expense is spared to furnish an index of literature and not of titles.

An Index of the World's Literature The original articles in over 200 of the better journals published in the principal countries of the world are listed in this index.

An Up-to-Date Index This index furnishes references to articles published UP TO THE TIME OF GOING TO PRESS.

For permanent reference, the fourth or last number for the year is bound in cloth.

PRICE—$4.00 per current year

AMERICAN MEDICAL ASSOCIATION

535 N. Dearborn St., Chicago, Ill.

Sign and Return This Coupon if You Wish to Subscribe

SPECIAL ORDER BLANK. American Medical Association, Chicago, Ill.

Gentlemen: Please enter my subscription for the **Quarterly Cumulative Index to Current Medical Literature** for this year (1919) and thereafter unless I order it discontinued. Enclosed please find check for $4.00 for 1919. (Remittance must accompany this order. Foreign postage 50 cents extra.)

Signed..... Address .....

Books from the Press of the American Medical Association

DISTURBANCES OF THE HEART

Second Edition—Revised and Enlarged

OLIVER T. OSBORNE, A.M., M.D.

The newer instrumental methods for the study of the heart, the polygraph, the electrocardiograph, etc., have resulted in a changed conception of the etiology and character of many heart disturbances, and compelled modifications in heart therapy. This book is a discussion of the newer findings from the point of view of the clinician, with special reference to treatment.

Physiologic and drug treatment are covered in a practical manner, and many valuable directions are given as to the management of cases and the regulation of the lives of patients having heart disturbances. Important chapters are those on Heart Disease in Children and During Pregnancy, Cardiovascular Renal Disease, Hypertension, etc. A section is devoted to a discussion of blood pressure. An index affords easy reference to any subject.

Flexible Red Cloth. 269 pp. Pocket size, 4⅝ by 7⅝ inches. Price, Postpaid, 75 cents

DISTURBANCES OF THE KIDNEY

OLIVER T. OSBORNE, M.D.

New Haven, Conn.

A little 209-page reprint volume written in simple, readable style and with particular reference to the therapeutics of kidney diseases. There are sixteen sections covering anatomy, physiology and function; abnormalities of the urine; albuminuria; renal calculi; hematuria; nephritis; acute nephritis (acute Bright's disease); chronic nephritis; uremia; pathologic condition and anomalies; ureteral catheterization and pyelography; pyelitis; tuberculosis of the kidney; tumors and cysts; the kidneys in pregnancy and disturbances of the bladder.

Silk Cloth. Size, 7⅝ by 4⅝. 209 pp. Price, Postpaid, 75 cents

SYPHILIS AS A MODERN PROBLEM

WILLIAM ALLEN PUSEY, M.D.

Professor of Dermatology in the University of Illinois, Chicago

This book is a separate reprint in monograph form of the article by William Allen Pusey in the Commemoration Volume issued as a tribute to the medical sciences which made possible the building of the Panama Canal. In this book, Dr. Pusey traces the history of syphilis, calls attention to its symptoms, and discusses the sociologic problems connected with this social disease. The work has been written primarily for the intelligent nonmedical reader, but will be appreciated by physicians.

Pages 129. Price, Postpaid, Paper, 50 cents. Price, Postpaid, Cloth, 75 cents

INFECTION AND IMMUNITY

VICTOR C. VAUGHAN, M.D.

Professor of Bacteriology and Hygiene in the University of Michigan

This book is a reprint in monograph form of the articles by Dr. Vaughan in the Commemoration Volume. It is a direct and reliable presentation of infection and immunity. Sections are devoted to the common infections and the subject is considered primarily from the standpoint of the layman rather than the physician. The latter, however, will find it to be an adequate summary of our modern knowledge of these new subjects.

Cloth. 238 pp. Price, $1.00

NEW AND NONOFFICAL REMEDIES

This is an official publication of the Council on Pharmacy and Chemistry of the American Medical Association. It contains descriptions of those preparations—proprietary and nonproprietary—acceptable to the Council on the date of publication. The description of each preparation includes the chief facts physicians desire to know concerning compositions, dosage, indications, cautions to be observed, etc.

The book also contains the rules of the Council which form the basis of the work.

Every physician who desires to further the cause of scientific prescribing and to aid in diminishing the domination of commercialism in therapeutics in this country should have a copy of this book for ready reference.

Single copy, cloth cover, postpaid, $1.00

THE PROPAGANDA FOR REFORM IN PROPRIETARY MEDICINES

Ninth Edition, Revised and Greatly Enlarged

As New and Nonofficial Remedies covers the field of worthy proprietaries, so the Propaganda for Reform covers the field of the unworthy. Interestingly, even entertainingly written, it contains an enormous amount of information that every physician needs. With New and Nonofficial Remedies and the Propaganda for Reform in his hands, the practitioner can tell what to choose among proprietary remedies—and why; what to avoid—and why. An exhaustive index makes the Propaganda for Reform practically an encyclopedia of unscientific, inefficient and fraudulent proprietaries.

Brown cloth, stamped in gold. 512 pages. Price, Postpaid, $1.00

LAWS

REGULATING THE PRACTICE OF MEDICINE IN THE UNITED STATES AND ELSEWHERE

A New and Completely Revised Edition is issued each year.

This book contains:

(1) Complete information about laws regulating practice in each state of the United States.

(2) A list of foreign medical colleges and brief statements concerning requirements to practice in foreign countries.

(3) Account of latest status of reciprocity in the United States.

From this handbook the physician can learn the essential features regarding practically every law regulating medical licensure and practice. The large sale which this book on laws has received since its first edition is good evidence that it is of inestimable value to the profession.

Paper cover. 230 pp. 5¼ by 8 inches. Price, Postpaid, 50 cents

SUGGESTIONS TO MEDICAL AUTHORS

Including Style Book of the A. M. A. Press and Guide to Bibliographic References.

This pamphlet contains valuable information in regard to the preparation of articles for publication and the points which make an article acceptable.

Paper Cover. 68 pp. Price, 25 Cents. American Medical Association, 535 North Dearborn St., Chicago

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to Dr. Joseph L. Miller, 122 South Michigan Boulevard, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy submitted. Zinc etchings, halftones and blocks for colored reproduction of illustrations will be supplied by the publisher when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index published by the American Medical Association. This requires, in the order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. On receipt of stamped addressed envelope, "Bibliographic Style," containing rules for footnotes and bibliographies, and a list of leading medical periodicals of the world, with approved abbreviations, will be sent. "Suggestions to Medical Authors," a comprehensive pamphlet on the preparation of medical manuscripts, which also includes "Bibliographic Style," will be sent on receipt of twenty-five cents.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright, but as a general thing, no objection will be made to its reproduction in reputable medical journals, if proper credit is given.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The domestic subscription price per year of two volumes is $5.00; Canadian rate, $5.25; foreign rate, $5.40 (23 shillings, 28 francs), including postage. Single copies, 50 cents, postpaid.

Make checks, etc., payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS

of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. $5 per annum. Single copies, 15 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. Includes reviews and a bibliographic index of pediatric subjects. Illustrated. $4 yearly. Single copies, 40 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature; book reviews, society transactions, etc. Illustrated. $5 per annum. Single copies, 50 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, etc. $5 per annum. Single copies, 50 cents.

QUARTERLY CUMULATIVE INDEX TO CURRENT MEDICAL LITERATURE—Quarterly. A complete subject and author index to the worthwhile current medical literature of the world. Issued four times a year. Fourth volume bound for permanent reference. Subscription price, $4 per current year.

For Clubbing Arrangements Address

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. - - - - - - - - CHICAGO

CONTENTS

PAGE

BOTULISM. A STUDY OF THE RESISTANCE OF THE SPORES OF BACILLUS BOTULINUS TO VARIOUS STERILIZING AGENCIES WHICH ARE COMMONLY EMPLOYED IN THE CANNING OF FRUITS AND VEGETABLES. ERNEST C. DICKSON, M.D., GEORGINA S. BURKE, A.M., AND ENGELENA S. WARD, A.M., SAN FRANCISCO 581

A STUDY OF PNEUMOCOCCUS CARRIERS. JOSEPH SAILER, M.D., PHILADELPHIA; MILTON W. HALL, M.D., CAMP JACKSON, S. C.; ROBERT L. WILSON, M.D., JEANNETTE, PA., AND CHARLES MCCOY, M.D., M. C., U. S. ARMY 600

ANTIPYRETICS. I. THE BENEDICT RESPIRATION CHAMBER AT THE NEW HAVEN HOSPITAL. HENRY G. BARBOUR, M.D., NEW HAVEN, CONN 611

ANTIPYRETICS. II. ACETYLSALICYLIC ACID AND HEAT REGULATION IN NORMAL INDIVIDUALS. HENRY G. BARBOUR, M.D., AND MICHAEL M. DEVENIS, M.D., NEW HAVEN, CONN 617

ANTIPYRETICS. III. ACETYLSALICYLIC ACID AND HEAT REGULATION IN FEVER CASES. HENRY G. BARBOUR, M.D., NEW HAVEN, CONN 624

MENTAL DISORDERS FOLLOWING INFLUENZA. ALFRED GORDON, M.D., PHILADELPHIA 633

THE ELECTROCARDIOGRAM AND VENTRICULAR PREPONDERANCE. EDWARD PERKINS CARTER, M.D., AND CARL H. GREENE, PH.D., BALTIMORE 638

THE BASAL METABOLISM IN EXOPHTHALMIC GOITER. J. H. MEANS, M.D., AND J. C. AUB, M.D., BOSTON 645

THE MORE COMMON GASES; THEIR EFFECT ON THE RESPIRATORY TRACT. OBSERVATION ON TWO THOUSAND CASES. ROBERT S. BERGHOFF, M.D., CHICAGO 678

INDEX TO VOLUME 24 685